MELANOCORTIN RECEPTOR LIGANDS

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CROSS REFERENCE TO RELATED APPLICATION

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/420,578, filed October 23, 2002.

FIELD OF THE INVENTION

The present invention relates to melanocortin (MC) receptor ligands that have a 4-substituted nitrogen atom-containing ring, which provides for enhanced activity. These ligands preferably exhibit selectivity for the MC-3 and/or MC-4 receptors relative to the other melanocortin receptors (in particular the MC-1 receptor) and are suitable for use in pharmaceutical compositions and in treatment methods.

BACKGROUND OF THE INVENTION

Melanocortin peptides (melanocortins) are natural peptide hormones in animals and man that bind to and stimulate MC receptors. Examples of melanocortins are α-MSH (melanocyte stimulating hormone), β-MSH, γ-MSH, ACTH (adrenocorticotropic hormone) and their peptide fragments. MSH is mainly known for its ability to regulate peripheral pigmentation, whereas ACTH is known to induce steroidoneogenesis. The melanocortin peptides also mediate a number of other physiological effects. They are reported to affect motivation, learning, memory, behavior, inflammation, body temperature, pain perception, blood pressure, heart rate, vascular tone, natriuresis, brain blood flow, nerve growth and repair, placental development, aldosterone synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, uterine bleeding in women, sebum and pheromone secretion, sexual activity, penile erection, blood glucose levels, intrauterine fetal growth, food motivated behavior, as well as other events related to parturition.

Both the MC-4 and MC-3 receptors have been localized to the hypothalamus, a region of the brain believed to be involved in the modulation of feeding behavior. Compounds showing selectivity for the MC-3/MC-4 receptors have been shown to alter food intake following intracerebroventricular and peripheral injection in rodents. Specifically, agonists have been shown to reduce feeding, while antagonists have been shown to increase feeding. The role of the MC-4 and MC-3 receptors have been defined in the control of body weight regulation in mammals. It is believed that the MC-3 receptor influences feed efficiency and the partitioning of

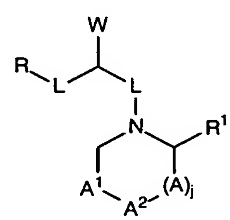
fuel stores into fat, whereas the MC-4 receptor regulates food intake and possibly energy expenditure. Thus, these receptor subtypes appear to reduce body weight through distinct and complementary pathways. Therefore compounds that stimulate both the MC-3 and MC-4 receptors may have a greater weight loss effect than those that are selective for either the MC-3 or MC-4 receptor.

Body weight disorders such as obesity, anorexia and cachexia are widely recognized as significant public health issues and there is a need for compounds and pharmaceutical compositions which can treat these disorders.

The Applicants have discovered a class of compounds that surprisingly have high affinity for the MC-4 and/or the MC-3 receptor subtypes, and that are typically selective for these MC receptors relative to the other melanocortin receptor subtypes, particularly the MC-1 subtype.

SUMMARY OF THE INVENTION

The present invention relates to compounds which comprise an alkyl substituted heterocyclic ring. The compounds, including all enantiomeric and diastereomeric forms and pharmaceutically acceptable salts thereof, have the formula:



wherein L represents a linking unit each of which is independently selected from the group consisting of:

a) $-(R^2)_p(CH{=}CH)_q-$;

b) $-(R^2)_y(X)_zC(Y)_w(X)_z(R^2)_y-$;

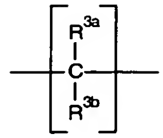
c) $-(R^2)_y(X)_zS(Y)_k(X)_z(R^2)_y-$;

d) $-(R^2)_y(Z)_mNR^4(Z)_m(R^2)_y-$;

e) $-(R^2)_y(O)_zP(T)_k(O)_z(R^2)_y-$;

wherein T is =O, $-OR^4$, and mixtures thereof; wherein X is –O–, –S–, $-NR^4-$; Y is =O, =S, $=NR^4$, $-R^4$, and mixtures thereof; Z is =N–, $-NR^4-$, and mixtures thereof; the index k is from 0 to 2; the index m is 0 or 1; the index p is from 0 to 12; the index q is from 0 to 3; the index w is from 0 to 2; the index y is 0 or 1; the index z is 0 or 1;

each R^2 is independently a substituted or unsubstituted methylene unit represented by the formula:



wherein R^{3a} and R^{3b} are each independently selected from the group consisting of:

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocycle;

g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof;

iii) $-[C(R^{11})_2]_nCOR^4$;

iv) $-[C(R^{11})_2]_nCOOR^4$;

v) $-[C(R^{11})_2]_nCOCH{=}CH_2$;

vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;

vii) $-[C(R^{11})_2]_nCON(R^4)_2$;

viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$

ix) $-[C(R^{11})_2]_nCN$;

x) $-[C(R^{11})_2]_nCNO$;

xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;

xii) $-[C(R^{11})_2]_nN(R^4)_2$;

xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C(=NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

xxxi) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

xxxii) an R^{3a} and an R^{3b} unit from the same carbon atom can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 8 atoms;

xxxiii) an R^{3a} or R^{3b} unit from a first R^2 unit can be taken together with an R^{3a} or R^{3b} unit from a second R^2 unit to form a carbocyclic or heterocyclic ring comprising from 3 to 8 atoms;

xxxiv) and mixtures thereof;

wherein R^4 units are the same as defined herein below, and any two R^4 units can be taken together to form a substituted or unsubstituted carbocyclic ring comprising from 3 – 8 carbon atoms; R^9 is R^4, fluorine, chlorine, bromine, iodine, and mixtures thereof; each R^{11} is hydrogen or R^{10}; the index n has the value from 0 to 10.

R^4 units are hydrocarbyl units each of which is independently selected from the group consisting of:

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocycle;

g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof;

iii) any two R^4 units can be taken together to form a substituted or unsubstituted carbocyclic ring comprising from 3 –8 carbon atoms;

R is a substituted or unsubstituted hydrocarbyl unit selected from the group consisting of:

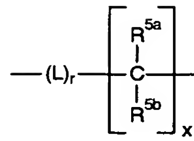
a) non-aromatic carbocyclic rings;

b) aromatic carbocyclic rings;

c) non-aromatic heterocyclic rings;

d) aromatic heterocyclic rings;

W is a pendant unit having the formula:



wherein the index r is 0 or 1, and the index x is from 0 to 10;

Q is:

a) hydrogen;
b) $-N(R^4)_2$;
c) $-OR^4$;
d) a unit which comprises a substituted or unsubstituted unit selected from the group consisting of:
   i) non-aromatic carbocyclic rings;
   ii) aromatic carbocyclic rings;
   iii) non-aromatic heterocyclic rings;
   iv) aromatic heterocyclic rings;

   wherein the number of rings is from 1 to 3;

R^{5a} and R^{5b} are each independently selected from the group consisting of

i) hydrogen;
ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:
   a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;
   b) C_3-C_{12} substituted or unsubstituted cycloalkyl;
   c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;
   d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;
   e) C_6-C_{12} substituted or unsubstituted aryl;
   f) C_1-C_{12} substituted or unsubstituted heterocyclic;
   g) C_3-C_{12} substituted or unsubstituted heteroaryl;
   h) and mixtures thereof;
iii) $-[C(R^{11})_2]_nCOR^4$;
iv) $-[C(R^{11})_2]_nCOOR^4$;
v) $-[C(R^{11})_2]_nCOCH{=}CH_2$;
vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;
vii) $-[C(R^{11})_2]_nCON(R^4)_2$;
viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$
ix) $-[C(R^{11})_2]_nCN$;
x) $-[C(R^{11})_2]_nCNO$;
xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;
xii) $-[C(R^{11})_2]_nN(R^4)_2$;
xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C(=NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

xxxi) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

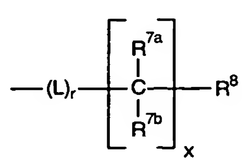
xxxii) R^{5a} and R^{5b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 10 atoms;

xxxiv) and mixtures thereof;

R^4 units are the same as defined herein above, and any two R^4 units can be taken together to form a substituted or unsubstituted carbocyclic ring comprising from 3 –8 carbon atoms; R^1 is substituted or unsubstituted C_1-C_{12} linear or branched alkyl, C_3-C_8 cyclic alkyl, C_2-C_{12} linear or branched alkenyl, or $-[C(R^9)_2]_nC(R^9)_3$; R^9 is hydrogen, fluorine, chlorine, bromine, iodine, and mixtures thereof; the index n has the value from 0 to 10 as defined herein above;

A, A^1, and A^2 are ring components each of which is independently selected from the group consisting of $-C(=NR^6)-$, $-C(=O)-$, $-C(=S)-$, $-C(R^6)_2-$, $-C(R^6)_2C(R^6)_2-$, $-CR^6=$, $-N=$, $-NR^6-$, or two A units can be taken together with an adjacent atom or A unit to form a bond having the formula $-N=N-$, $-N-NR^6-$, $-CR^6=N-$, $-C=N-$, and mixtures thereof; the index j is 0 or 1;

R^6 is hydrogen, R^4, or the pendant unit W^1 having the formula:



wherein the index r is equal to 0 or 1;

R^{7a} and R^{7b} are each independently selected from the group consisting of

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocyclic;

g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof;

iii) $-[C(R^{11})_2]_nCOR^4$;

iv) $-[C(R^{11})_2]_nCOOR^4$;

v) $-[C(R^{11})_2]_nCOCH{=}CH_2$;

vi) $-[C(R^{11})_2]_nC({=}NR^4)N(R^4)_2$;

vii) $-[C(R^{11})_2]_nCON(R^4)_2$;

viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$

ix) $-[C(R^{11})_2]_nCN$;

x) $-[C(R^{11})_2]_nCNO$;

xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;

xii) $-[C(R^{11})_2]_nN(R^4)_2$;

xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C({=}NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

xxxi) haloalkyl having the formula $–[C(R^9)_2]_nC(R^9)_3$;

xxxii) and mixtures thereof;

R^8 is selected from the group consisting of:

i) hydrogen;

ii) C_3-C_8 non-aromatic carbocyclic rings;

iii) C_6-C_{14} aromatic carbocyclic rings;

iv) C_1-C_7 non-aromatic heterocyclic rings;

v) C_3-C_{13} aromatic heterocyclic rings;

vi) $-C(Y)R^4$;

vii) $-C(Y)_2R^4$;

viii) $-C(Y)N(R^4)_2$;

ix) $-C(Y)NR^4N(R^4)_2$;

x) -CN;

xi) -CNO;

xii) $-[C(R^9)_2]C(R^9)_2$;

xiii) $-N(R^4)_2$;

xiv) $-NR^4CN$;

xv) $-NR^4C(Y)R^4$;

xvi) $-NR^4C(Y)N(R^4)_2$;

xvii) $-NHN(R^4)_2$;

xviii) $-NHOR^4$;

xix) -NCS;

xx) $-NO_2$;

xxi) $-OR^4$;

xxii) -OCN;

xxiii) $-OCF_3$, $-OCCl_3$, $-OCBr_3$;

xxiv) -F, -Cl, -Br, -I, and mixtures thereof;

xxv) -SCN;

xxvi) $-SO_3M$;

xxvii) $-OSO_3M$;

xxviii) $-SO_2N(R^4)_2$;

xxix) $-SO_2R^4$;

xxx) $-P(O)M_2$;

xxxi) $-PO_2$;

xxxii) $-P(O)(OM)_2$;

xxxiii) and mixtures thereof

wherein R^4 units are the same as defined herein above, and any two R^4 units can be taken together to form a substituted or unsubstituted carbocyclic ring comprising from 3 –8 carbon atoms.

These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{O} C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

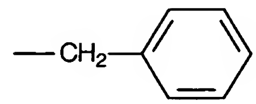
The present invention relates to melanocortin (MC) receptor ligands. The melanocortin (MC) class of peptides mediates a wide range of physiological effects. Synthetic peptides and peptide mimetics, which modulate the interaction of natural MC ligands have varying degrees of selectivity and binding. The present invention is directed to ligands that are selective for the MC4 receptor, or that are selective for both the MC4 and MC3 receptor while minimizing the interaction at the MC1, MC2, and MC5 receptors.

For the purposes of the present invention the term "hydrocarbyl" is defined herein as any organic unit or moiety which is comprised of carbon atoms and hydrogen atoms. Included within the term hydrocarbyl are the heterocycles which are described herein below. Examples of various unsubstituted non-heterocyclic hydrocarbyl units include pentyl, 3-ethyloctanyl, 1,3-dimethylphenyl, cyclohexyl, cis-3-hexyl, 7,7-dimethylbicyclo[2.2.1]-heptan-1-yl, and naphth-2-yl.

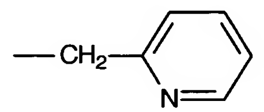
Included within the definition of "hydrocarbyl" are the aromatic (aryl) and non-aromatic carbocyclic rings, non-limiting examples of which include cyclopropyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cyclohexenyl, cycloheptanyl, bicyclo-[0.1.1]-butanyl, bicyclo-[0.1.2]-pentanyl, bicyclo-[0.1.3]-hexanyl (thujanyl), bicyclo-[0.2.2]-hexanyl, bicyclo-[0.1.4]-heptanyl (caranyl), bicyclo-[2.2.1]-heptanyl (norboranyl), bicyclo-[0.2.4]-octanyl (caryophyllenyl), spiropentanyl, diclyclopentanespiranyl, decalinyl, phenyl, benzyl, naphthyl, indenyl, 2H-indenyl, azulenyl, phenanthryl, anthryl, fluorenyl, acenaphthylenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The term "heterocycle" includes both aromatic (heteroaryl) and non-aromatic heterocyclic rings non-limiting examples of which include: pyrrolyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrazolyl, 2H-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazoyl, 1,2,4-oxadiazolyl, 2H-pyranyl, 4H-pyranyl, 2H-pyran-2-one-yl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, s-triazinyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, oxepinyl, 4H-1,2-diazepinyl, indenyl 2H-indenyl, benzofuranyl, isobenzofuranyl, indolyl, 3H-indolyl, 1H-indolyl, benzoxazolyl, 2H-1-benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, 2H-1,4-benzoxazinyl, pyrrolidinyl, pyrrolinyl, quinoxalinyl, furanyl, thiophenyl, benzimidazolyl, and the like each of which can be substituted or unsubstituted.

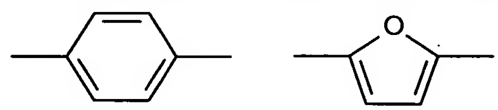
An example of a unit defined by the term "alkylenearyl" is a benzyl unit having the formula:



whereas an example of a unit defined by the term "alkyleneheteroaryl" is a 2-picolyl unit having the formula:



The terms "arylene" and "heteroarylene" relate to aryl and heteroaryl units which can serve as part of a linking group, for example, units having the formula:



which represent an arylene and heteroarylene unit respectively.

The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "encompassing moieties or units which can replace a hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety. Also substituted can include replacement of hydrogen atoms on two adjacent carbons to form a new moiety or unit." For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. An epoxide unit is an example of a substituted unit which requires replacement of a hydrogen atom on adjacent carbons. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain, can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit."

The following are non-limiting examples of units, herein after also indicated as R^{10}, which can serve as a replacement for hydrogen atoms when a hydrocarbyl unit is described as "substituted." Non-limiting examples of R^{10} include:

i) $-[C(R^4)_2]_p(CH{=}CH)_qR^4$; wherein p is from 0 to 12; q is from 0 to 12;

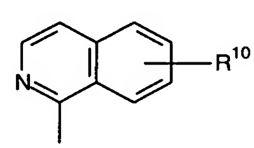
ii) $-[C(R^{11})_2]_nC(X)R^4$;

iii) $-[C(R^{11})_2]_nC(X)_2R^4$;

iv) $-[C(R^{11})_2]_nC(X)CH{=}CH_2$;

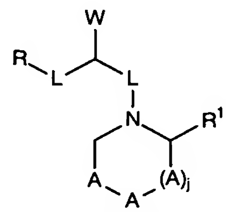
v) $-[C(R^{11})_2]_nC(X)N(R^4)_2$;
vi) $-[C(R^{11})_2]_nC(X)NR^4N(R^4)_2$;
vii) $-[C(R^{11})_2]_nCN$;
viii) $-[C(R^{11})_2]_nCNO$;
ix) $-CF_3$, $-CCl_3$, $-CBr_3$;
x) $-[C(R^{11})_2]_nN(R^4)_2$;
xi) $-[C(R^{11})_2]_nNR^4CN$;
xii) $-[C(R^{11})_2]_nNR^4C(X)R^4$;
xiii) $-[C(R^{11})_2]_nNR^4C(X)N(R^4)_2$;
xiv) $-[C(R^{11})_2]_nNHN(R^4)_2$;
xv) $-[C(R^{11})_2]_nNHOR^4$;
xvi) $-[C(R^{11})_2]_nNCS$;
xvii) $-[C(R^{11})_2]_nNO_2$;
xviii) $-[C(R^{11})_2]_nOR^4$;
xix) $-[C(R^{11})_2]_nOCN$;
xx) $-[C(R^{11})_2]_nOCF_3$, $-OCCl_3$, $-OCBr_3$;
xxi) -F, -Cl, -Br, -I, and mixtures thereof;
xxii) $-[C(R^{11})_2]_nSCN$;
xxiii) $-[C(R^{11})_2]_nSO_3M$;
xxiv) $-[C(R^{11})_2]_nOSO_3M$;
xxv) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;
xxvi) $-[C(R^{11})_2]_nSO_2R^4$;
xxvii) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;
xxviii) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;
xxix) and mixtures thereof;

wherein R^4 and R^{11} are defined herein below; M is hydrogen, or a salt forming cation; X is defined herein below. Suitable salt forming cations include, sodium, lithium, potassium, calcium, magnesium, ammonium, and the like. Non-limiting examples of an alkylenearyl unit include benzyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl. For the purposes of the present invention the term "substituted" on a chemical formula bearing an R^{10} moiety, for example the formula:



will stand equally well for the substitution of one or more hydrogen atoms.

The compounds of the present invention include all enantiomeric and diastereomeric forms and pharmaceutically acceptable salts of compounds having the core scaffold represented by the formula:

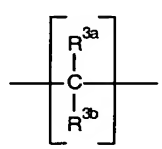


wherein L represents a linking unit each of which is independently selected from the group consisting of:

a) $-(R^2)_p(CH{=}CH)_q-$;
b) $-(R^2)_y(X)_zC(Y)_w(X)_z(R^2)_y-$;
c) $-(R^2)_y(X)_zS(Y)_k(X)_z(R^2)_y-$;
d) $-(R^2)_y(Z)_mNR^4(Z)_m(R^2)_y-$;
e) $-(R^2)_y(O)_zP(T)_k(O)_z(R^2)_y-$;

wherein T is =O, -OR^4, and mixtures thereof; wherein X is –O–, –S–, –NR^4–; Y is =O, =S, =NR^4, –R^4, and mixtures thereof; Z is =N–, –NR^4–, and mixtures thereof; the index k is from 0 to 2; the index m is 0 or 1; the index p is from 0 to 12; the index q is from 0 to 3; the index w is from 0 to 2; the index y is 0 or 1; the index z is 0 or 1.

Each R^2 is independently a substituted or unsubstituted methylene unit represented by the formula:



wherein R^{3a} and R^{3b} are each independently selected from the group consisting of:

i) hydrogen;
ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:
  a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;
  b) C_3-C_{12} substituted or unsubstituted cycloalkyl;
  c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;
  d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;
  e) C_6-C_{12} substituted or unsubstituted aryl;
  f) C_1-C_{12} substituted or unsubstituted heterocyclic;
  g) C_3-C_{12} substituted or unsubstituted heteroaryl;
  h) and mixtures thereof;
iii) -$[C(R^{11})_2]_nCOR^4$;

iv) $-[C(R^{11})_2]_nCOOR^4$;

v) $-[C(R^{11})_2]_nCOCH=CH_2$;

vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;

vii) $-[C(R^{11})_2]_nCON(R^4)_2$;

viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$

ix) $-[C(R^{11})_2]_nCN$;

x) $-[C(R^{11})_2]_nCNO$;

xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;

xii) $-[C(R^{11})_2]_nN(R^4)_2$;

xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C(=NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

xxxi) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

xxxii) an R^{3a} and an R^{3b} unit from the same carbon atom can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 8 atoms;

xxxiii) an R^{3a} or R^{3b} unit from a first R^2 unit can be taken together with an R^{3a} or R^{3b} unit from a second R^2 unit to form a carbocyclic or heterocyclic ring comprising from 3 to 8 atoms;

xxxiv) and mixtures thereof;

R^9 is R^4, fluorine, chlorine, bromine, iodine, and mixtures thereof; each R^{11} is hydrogen or R^{10}; the index n has the value from 0 to 10.

R^4 units are hydrocarbyl units each of which is independently selected from the group consisting of:

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocyclic;

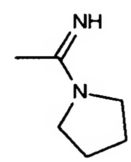
g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof.

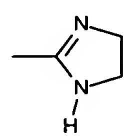
Throughout the present specification whenever two or more R^4 units comprise a moiety as herein above, any two of said R^4 units can be taken together to form a substituted or unsubstituted carbocyclic ring comprising from 3 –8 carbon atoms, for example, a unit having the formula:

vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;

can represent a unit having the formula:



or a unit having the formula:



One aspect of the linking units relates to peptide and peptide mimetic linking groups each of which are independently selected from units which are represented by the formula:

$$-(R^2)_y(X)_zC(Y)_w(X)_z(R^2)_y-$$

wherein X is $-NR^4-$; Y is =O, $=NR^4$, and mixtures thereof, specific embodiments of which include L units selected from the group consisting of $-CH_2NR^4CH_2-$; $-NR^4-$; $-NR^4CH_2-$; $-NR^4C(O)NR^4-$; $-NR^4C(=NR^4)NR^4-$.

Non-limiting examples of this aspect include a urea unit having the formula:

$$-NHC(O)NH-$$

an amide unit having the formula:

$$-NHC(O)-$$

or the formula:

$$-NHC(O)R^2-$$

wherein R^2 is C_1-C_4 alkylene;

an amine unit having the formula:

$$-NHR^2-$$

wherein R^2 is C_1-C_4 alkylene;

and a guanidine unit having the formula:

$$-NHC(=NR^4)NH-$$

wherein R^4 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, isopentyl, benzyl, and mixtures thereof.

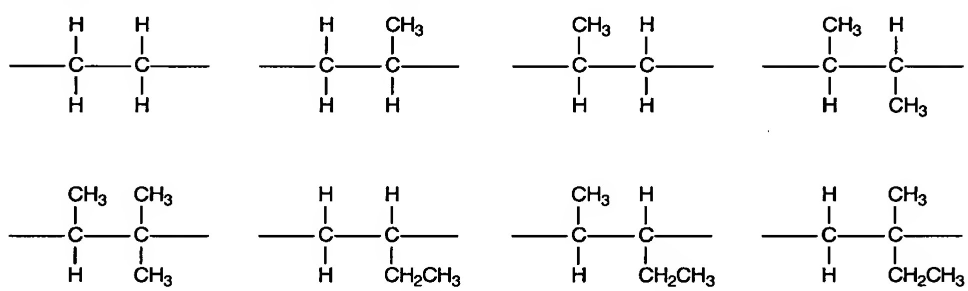
A second aspect of the linking groups of the present invention relates to linking units having the formula:

a) $-(R^2)_p(CH=CH)_q-$;

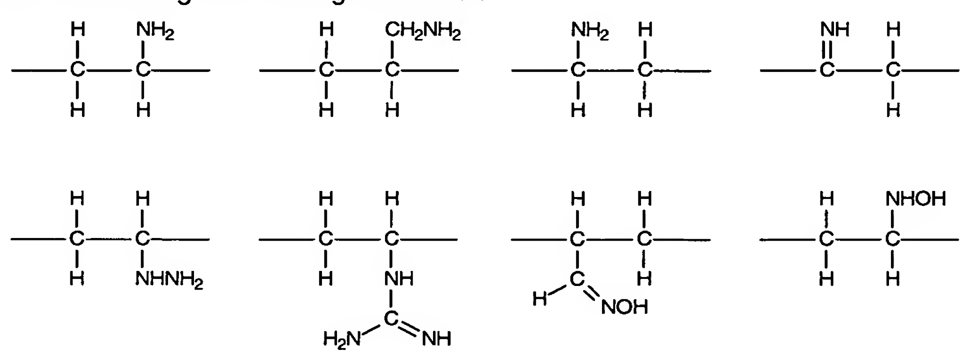
wherein the index q is 0 and the index p is 2 or greater thereby providing linking units having the formula:

$$-[C(R^{3a})(R^{3b})]_2-$$

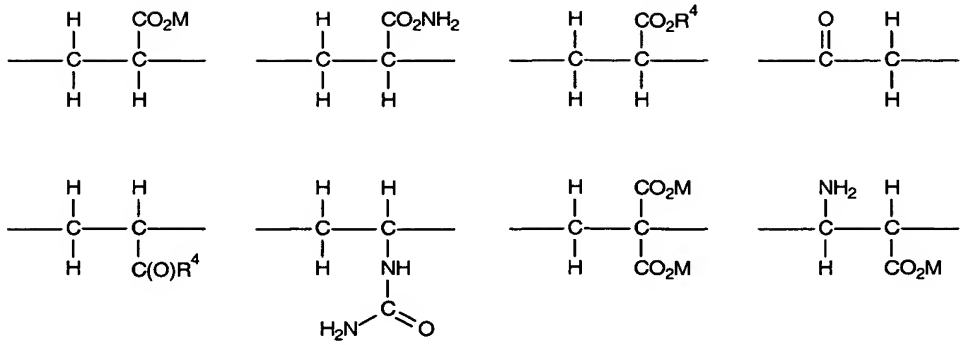
a first iteration of which relates to linking groups formed when the index p is equal to 2, non-limiting examples of which have the formula:



Another iteration of this aspect of linking units relates to L units which comprise one or more R^{3a} and R^{3b} units which can form a hydrogen bond, non-limiting examples of which include nitrogen atom containing units having the formula:



Another iteration of this aspect of the linking groups relates to R^{3a} and R^{3b} units which comprise a carbonyl unit, non-limiting examples of which include units having the formula:



A further aspect of L relates to sulfonamide linking unit having the formula:

$$-NHSO_2-$$

said unit providing one aspect of W units as defined herein below.

The scaffolds for several of the Categories of melanocortin receptor ligands of the present invention comprise linking units, L, selected from the group consisting of:

i) -C(O)-;

ii) $-CH_2-$;

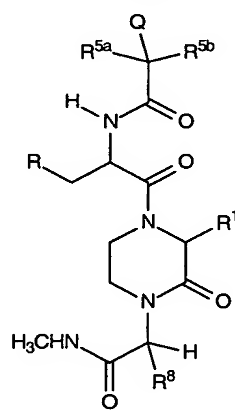
iii) -NH-;

iv) -HNC(O)-;

v) -C(O)NH-; and

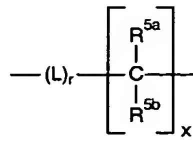
vi) -O-.

For example, melanocortin receptors ligands, which comprise the first aspect of Category II compounds as described further herein below, have the formula:



and utilize the linking units -C(O)-; $-CH_2-$; and -HNC(O)-. The formulator may select among any of the herein described linking units to connect or tether the functional units comprising the compounds of the present invention.

W is a pendant unit having the formula:



wherein the index r is 0 or 1 and the index x is from 0 to 10.

Q is:

a) hydrogen;

b) $-N(R^4)_2$;

c) $-OR^4$;

d) a unit which comprises a substituted or unsubstituted unit selected from the group consisting of:

i) non-aromatic carbocyclic rings;

ii) aromatic carbocyclic rings;

iii) non-aromatic heterocyclic rings;

iv) aromatic heterocyclic rings;

wherein the number of rings is from 1 to 3;

R^{5a} and R^{5b} are each independently selected from the group consisting of

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocyclic;

g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof;

iii) $-[C(R^{11})_2]_nCOR^4$;

iv) $-[C(R^{11})_2]_nCOOR^4$;

v) $-[C(R^{11})_2]_nCOCH{=}CH_2$;

vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;

vii) $-[C(R^{11})_2]_nCON(R^4)_2$;

viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$

ix) $-[C(R^{11})_2]_nCN$;

x) $-[C(R^{11})_2]_nCNO$;

xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;

xii) $-[C(R^{11})_2]_nN(R^4)_2$;

xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C(=NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

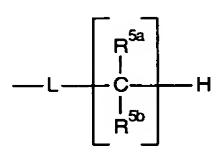
xxxi) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

xxxii) R^{5a} and R^{5b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 10 atoms;

xxxiv) and mixtures thereof;

R^9 is R^4, fluorine, chlorine, bromine, iodine, and mixtures thereof; each R^{11} is hydrogen or R^{10}; the index n has the value from 0 to 10.

The first aspect of W comprises units having the formula:



wherein Q is hydrogen. A first iteration of this aspect utilizes the amide and amine linking units for L:

i) $-NHC(O)-$;

ii) $-NHC(O)CH_2-$; and

iii) $-NHCH_2-$;

which, when taken together with R^{5a} and R^{5b} units equal to hydrogen or C_1-C_4 linear or branched hydrocarbyl, provide W units which comprise alkyl and alkenyl amides and amines. Non-limiting examples of these alkyl and alkenyl amides and amines which comprise the first iteration of the first aspect of W units includes:

i) $-NHC(O)CH_3$;

ii) $-NHC(O)CH_2CH_3$;

iii) $-NHC(O)(CH_2)_2CH_3$;

iv) $-NHC(O)CH(CH_3)_2$;

v) $-NHC(O)CH(CH_3)CH_2CH_3$;

vi) $-NHC(O)CH_2CH(CH_3)_2$;

vii) $-NHC(O)(CH_2)_3CH_3$;

viii) $-NHC(O)CH_2CH{=}CHCH_3$; and

xix) $-NHC(O)CH_2CH_2CH{=}CH_2$.

A second iteration of this aspect relates to R^{5a} and R^{5b} units said units also include from the definitions of R^{5a} and R^{5b} units above, the units:

iii) $-COR^4$;

xii) $-N(R^4)_2$; and

xx) $-OR^4$;

wherein R^4 is hydrogen and C_1-C_4 alkyl. Non-limiting examples of this iteration of the first aspect of W units include:

i) $-NHC(O)CH(NH_2)CH_3$;

ii) $-NHC(O)CH(NHCH_3)CH_3$;

iii) $-NHC(O)CH[N(CH_3)_2]CH_3$;

iv) $-NHC(O)CH_2CH(NH_2)CH_3$;

v) $-NHC(O)CH_2CH(NHCH_3)CH_3$;

vi) $-NHC(O)CH(OH)CH_3$;

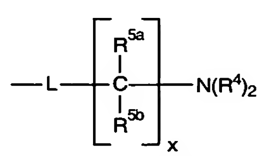
vii) $-NHC(O)CH(OCH_3)CH_3$;

viii) $-NHC(O)CH_2CH(OH)CH_3$;

xix) $-NHC(O)CH_2CH(OCH_3)CH_3$; and

x) $-NHC(O)CH_2CH(OH)CH(OH)CH_3$.

The second aspect of W comprises units having the formula:



wherein Q is $-N(R^4)_2$ and the index x is 1 or 2. A first iteration of this aspect utilizes the amide and amine linking units for L:

i) $-NHC(O)-$;

ii) $-NHC(O)CH_2-$; and

iii) $-NHCH_2-$;

which, when taken together with R^{5a} and R^{5b} units equal to hydrogen or C_1-C_4 linear or branched hydrocarbyl, provide W units which comprise alkyl and alkenyl amides and amines. Non-limiting examples of these alkyl and alkenyl amides and amines which comprise the first iteration of the second aspect of W units includes:

i) $-NHC(O)CH_2NH_2$;

ii) $-NHC(O)CH_2NHCH_3$;

iii) $-NHC(O)CH_2N(CH_3)_2$;

iv) $-NHC(O)CH(CH_3)NH_2$;

v) $-NHC(O)C(CH_3)_2NH_2$;

vi) $-NHC(O)CH(CH_3)NHCH_3$;

vii) $-NHC(O)CH(CH_3)N(CH_3)_2$; and

viii) $-NHC(O)C(CH_3)_2N(CH_3)_2$.

A second iteration of this aspect relates to R^{5a} and R^{5b} units said units also include from the definitions of R^{5a} and R^{5b} units above, the units:

iii) $-COR^4$;

xii) $-N(R^4)_2$; and

xx) $-OR^4$;

wherein R^4 is hydrogen and C_1-C_4 alkyl. Non-limiting examples of this iteration of the second aspect of W units include:

i) $-NHC(O)CH_2CH(NH_2)_2$; (x = 2)

ii) $-NHC(O)CH(CH_3)CH(NH_2)_2$; (x = 2)

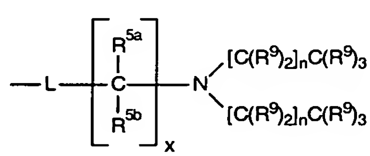
iii) $-NHC(O)CH(CH_2CH_2OH)CH_2NH_2$; (x = 2)

iv) $-NHC(O)CH_2CH(CH_3)NH_2$; (x = 2)

v) $-NHC(O)C(CH_3)(CH_2CH_3)NH_2$; (x = 1) and

vi) $-NHC(O)C(CH_2CH_3)_2NH_2$; (x = 1).

The third aspect of W units according to the present invention relates to units having the formula:



wherein Q is $-N(R^4)_2$, R^4 is $-[C(R^9)_2]_nC(R^9)_3$; the index n is from 0 to 10; and the index x is 1 or 2. A first iteration of this aspect utilizes the amide and amine linking units for L:

i) $-NHC(O)-$;

ii) $-NHC(O)CH_2-$; and

iii) $-NHCH_2-$;

non-limiting examples of this iteration of the third aspect of W units include:

i) $-NHC(O)CFH_2$;

ii) $-NHC(O)CF_2H$;

iii) $-NHC(O)CF_3$;

iv) $-NHC(O)CH_2CF_2H$;

v) $-NHC(O)CH_2CF_3$; and

vi) $-NHC(O)CClH_2$.

A second iteration of this aspect utilizes the amine linking unit for L:

i) –NH–;

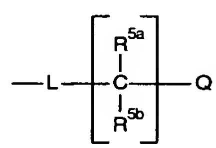
non-limiting examples of this iteration of the third aspect of W units include:

i) $-NHCFH_2$;

ii) $-NHCF_2H$; and

iii) $-NHCF_3$.

The fourth aspect of W units according to the present invention relates to units having the formula:



wherein L can comprise any iteration of the linking unit $-(X)_zC(Y)_w(X)_z-$ wherein each X is –NH–; Y is =O or =NH; each index z is independently 0 or 1; the index w is 1 or 2; R^{5a} and R^{5b} are each independently:

i) hydrogen;

ii) $-COR^4$;

iii) $-COOR^4$;

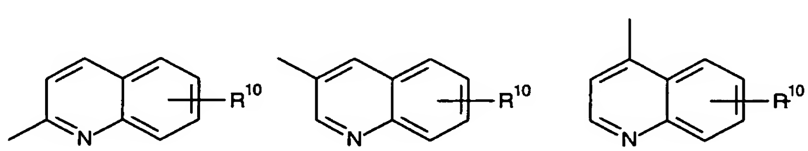
iv) $-N(R^4)_2$;

v) $-CON(R^4)_2$; or

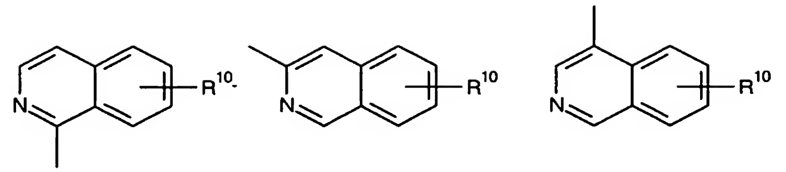
vi) $-NHCOR^4$;

and Q units are heterocycles comprising from 4 to 9 carbon atoms.

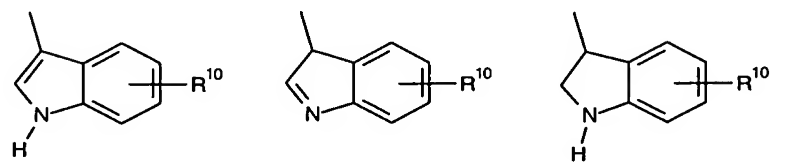
The first iteration of Q units according to the third aspect of W units relates to substituted and unsubstituted quinolin-2-yl, quinolin-3-yl, and quinolin-4-yl units having the formula:



The second iteration of Q units according to the third aspect of W units relates to substituted and unsubstituted isoquinolin-1-yl, isoquinolin-3-yl, and 1soquinolin-4-yl units having the formula:

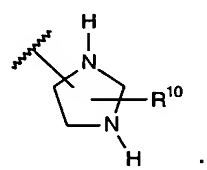


The third iteration of Q units according to the third aspect of W units relates to substituted and unsubstituted [5,6] fused ring systems, *inter alia*, 1*H*-indolin-3-yl having the formula:

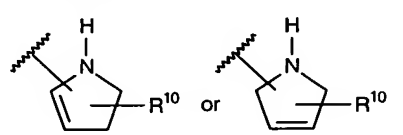


The fourth iteration of Q units according to the third aspect of W units relates to substituted and unsubstituted, saturated and unsaturated 5-member nitrogen containing rings selected from the group consisting of:

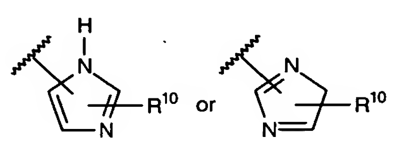
i) imidazolidines having the formula:



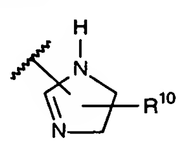
ii) pyrrolines having the formula:



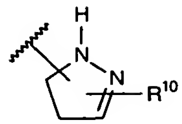
iii) imidazoles having the formula:



iv) imidazolines having the formula:

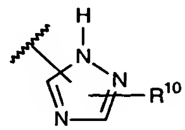


v) pyrazolines having the formula:



; and

vi) 1*H*-[1,2,4]triazoles having the formula:

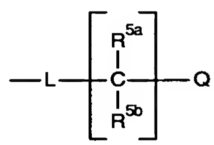


;

wherein any of the above Q units can optionally be bonded through or substituted at a nitrogen atom.

The fifth iteration of the fourth aspect of Q units relates to heterocycles which comprise more than one type of heteroatom or which are saturated ring, non-limiting examples of which include, morpholine, piperazine, pyrrolidine, dioxane, imidazoline, pyrazolidine, piperidine, and the like.

The fifth aspect of W units according to the present invention relates to units having the formula:



wherein L comprises linking units having the formula:

a) $-[C(R^3)_2]_p(CH{=}CH)_q-$; or

b) $-(X)_zC(Y)_w(X)_z-$;

wherein each X is –NH–; Y is =O or =NH; the index p is from 0 to 12; the index q is 0 or 1; each index z is independently 0 or 1; the index w is 1 or 2; R^{5a} and R^{5b} are each independently:

i) hydrogen;

ii) $-COR^4$;

iii) $-COOR^4$;

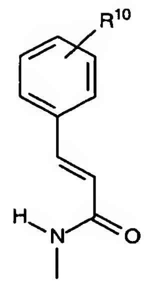
iv) $-N(R^4)_2$;

v) $-CON(R^4)_2$; or

vi) $-NHCOR^4$;

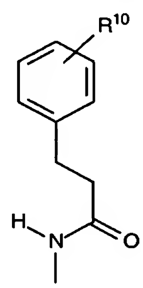
and Q units are substituted or unsubstituted carbocyclic or substituted or unsubstituted aryl units comprising from 4 to 12 carbon atoms.

The first iteration of this aspect relates to W units having the formula:



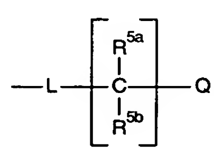
wherein R^{10} comprises one or more substitutions for hydrogen, said substitutions selected from the group consisting of fluoro, chloro, bromo, iodo, hydroxyl, methyl, trifluoromethyl, and methoxy. Non-limiting examples of W units which comprise this first iteration of the fifth aspect of W units include, 3-(4-hydroxyphenyl)-acrylamido, 3-(4-fluorophenyl)-acrylamido, 3-(4-chlorophenyl)-acrylamido, and the like. This aspect also includes the unsubstituted example, 3-phenyl-acrylamido.

The second iteration of this aspect relates to W units having the formula:



wherein R^{10} comprises one or more substitutions for hyrdrogen, said substitutions selected from the group consisting of fluoro, chloro, bromo, iodo, hydroxyl, methyl, trifluoromethyl, and methoxy. Non-limiting examples of W units which comprise this first iteration of the fifth aspect of W units include, 3-(4-hydroxyphenyl)-propionamido, 3-(4-fluorophenyl)-propionamido, 3-(4-chlorophenyl)-propionamido, and the like. This aspect also includes the unsubstituted example, 3-phenyl-propionamido.

The sixth aspect of W units according to the present invention relates to units having the formula:



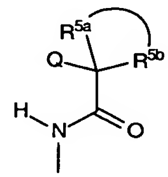
wherein L can comprise any iteration of the linking unit $-(X)_zC(Y)_w(X)_z-$ wherein each X is –NH–; Y is =O or =NH; each index z is independently 0 or 1; the index w is 1 or 2; R^{5a} and R^{5b} are each independently:

i) hydrogen; or

ii) C_1-C_{10} substiuted or unsubstitued, linear, branched or cyclic hydrocarbyl;

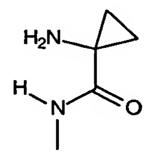
and Q units are heterocycles comprising from 4 to 9 carbon atoms as described for the fourth aspect of Q.

The eighth aspect of W units comprises units having the formula:



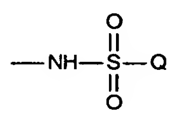
wherein R^{5a} and R^{5b} are taken together to form a ring selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

A first iteration of this aspect relates to units wherein Q is $-NH_2$ non-limiting examples of which include W units having the formula:



which are further exemplified herein below.

The ninth aspect of W units comprises sulfonamide linking units, said W units having the formula:



R is a substituted or unsubstituted hydrocarbyl unit selected from the group consisting of:

a) non-aromatic carbocyclic rings;

b) aromatic carbocyclic rings;

c) non-aromatic heterocyclic rings;

d) aromatic heterocyclic rings;

wherein said units which substitute for hydrogen on the rings which comprise R units are selected from the group consisting of:

i) C_1-C_{20} linear or branched, substituted or unsubstituted hydrocarbyl;

ii) halogen;

iii) $-N(R^4)_2$;

iv) $-COR^4$;

v) $-COOR^4$;

vi) cyano;

vii) nitro;

viii) hydroxyl;

ix) C_1-C_4 alkoxy;

x) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

xi) and mixtures thereof;

wherein R^4, R^9 and the index n are defined herein above.

A first aspect of R units relates to substituted and non-substituted aryl units, said units comprising phenyl, benzyl, naphthylen-2-yl, and naphthylen-2-ylmethyl.

A first iteration of this aspect encompasses R units which are selected from the group consisting of phenyl, 3-fluorophenyl, 4-fluorophenyl, 3,5-difluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 4-methylphenyl, and 4-acetoxyphenyl.

A second iteration of this aspect encompasses R units which are selected from the group consisting of naphthylen-1-yl, 2-naphthylen-2-yl, naphthalen-1-ylmethyl, naphthalen-2-ylmethyl, and 1-hydroxynaphthalen-2-ylmethyl.

A second aspect of R units relates to substituted and non-substituted heteroaryl units wherein R units comprise substituted or unsubstituted quinolinyl, isoquinolinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl.

A fist iteration of this aspect encompasses R units which are 1,2,3,4-tetrahydro-isoquinolinyl and 1,2,3,4-tetrahydroquinolinyl.

A second iteration of this aspect encompasses R units which are 6-hydroxy-1,2,3,4-tetrahydroisoquinolinyl and 6-hydroxy-1,2,3,4-tetrahydroquinolinyl.

Another aspect of R relates to phenyl rings comprising a C_1-C_4 alkyl unit, non-limiting examples or which include 4-methylphenyl, 2,4-dimethylphenyl, as well as mixed alkyl rings, *inter alia*, 2-methyl-4-isopropyl.

A yet further aspect of R relates to substituted or unsubstituted heteroaryl rings selected from the group consisting of thiophenyl, furanyl, oxazolyl, thiazolyl, pyrrolyl, and pyridinyl.

R^1 is a substituted or unsubstituted unit selected form the group consisting of:

i) C_1-C_{12} linear or branched alkyl;

ii) C_3-C_8 cyclic alkyl;

iii) C_2-C_{12} linear or branched alkenyl; and

iv) $-[C(R^9)_2]_nC(R^9)_3$.

Wherein R^9 is hydrogen, fluorine, chlorine, bromine, iodine, and mixtures thereof; and the units which can substitute for hydrogen are defined herein above; the index n has the value from 0 to 10.

A first aspect of R^1 relates to unsubstituted lower alkyl (C_1-C_4) R^1 units, for example, methyl, ethyl, iso-propyl, n-propyl, n-butyl, 2-butyl (1-methylpropyl), allyl, and the like.

A second aspect of R^1 relates to the unsubstituted C_5-C_8 linear alkyl units: n-pentyl, n-hexyl, n-heptyl, and n-octyl.

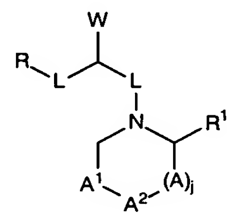
A third aspect of R^1 relates to unsubstituted cyclic alkyl, for example, cyclopropyl, 2-methyl-cyclopropyl, cyclopropylmethyl, cyclobutyl, 2-methylcyclobutyl, 3-methylcyclobutyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, and the like.

A fourth aspect of R^1 relates to substituted units which are haloalkyl units, for example, a first iteration relates to R^1 units selected from the group consisting of $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, and $-CCl_3$.

A fifth aspect of R^1 relates to substituted lower alkyl units. A first iteration of this aspect relates to R^1 units which are substituted with alkoxy units, for example, R^1 units selected from the group consisting of methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, and propoxypropyl.

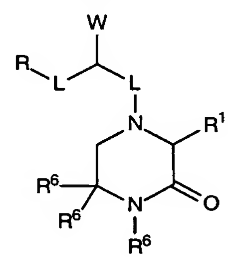
Melanocortin Receptor Ligand Ring Scaffolds

The scaffolds of the present invention, represented by the formula:



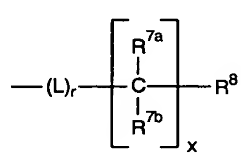
each comprise a nitrogen-containing ring, said ring further comprising A, A^1, and A^2 ring components each of which is independently selected from the group consisting of $-C(=NR^6)-$, $-C(=O)-$, $-C(=S)-$, $-C(R^6)_2-$, $-C(R^6)_2C(R^6)_2-$, $-CR^6=$, $-N=$, $-NR^6-$, or two A units can be taken together with an adjacent atom or another A unit to form a bond having the formula $-N=N-$, $-N-NR^6-$, $-CR^6=N-$, $-C=N-$, and mixtures thereof; the index j is equal to 0 or 1.

For example, A comprises $-C(=O)-$, A^1 unit comprises $-C(R^6)_2-$, and A^2 unit comprises $-NR^6-$, thereforeproviding a keto-piperazine scaffold having the formula:



wherein R^6 is defined herein below.

R^6 is hydrogen, R^4, or the pendant unit W^1 having the formula:



wherein the index r is equal to 0 or 1;

R^{7a} and R^{7b} are each independently selected from the group consisting of

i) hydrogen;

ii) C_1-C_{12} hydrocarbyl selected from the group consisting of:

a) C_1-C_{12} linear or branched, substituted or unsubstituted alkyl;

b) C_3-C_{12} substituted or unsubstituted cycloalkyl;

c) C_2-C_{12} linear or branched, substituted or unsubstituted alkenyl;

d) C_3-C_{12} substituted or unsubstituted cycloalkenyl;

e) C_6-C_{12} substituted or unsubstituted aryl;

f) C_1-C_{12} substituted or unsubstituted heterocyclyl;

g) C_3-C_{12} substituted or unsubstituted heteroaryl;

h) and mixtures thereof;

iii) $-[C(R^{11})_2]_nCOR^4$;

iv) $-[C(R^{11})_2]_nCOOR^4$;

v) $-[C(R^{11})_2]_nCOCH{=}CH_2$;

vi) $-[C(R^{11})_2]_nC(=NR^4)N(R^4)_2$;

vii) $-[C(R^{11})_2]_nCON(R^4)_2$;

viii) $-[C(R^{11})_2]_nCONR^4N(R^4)_2$

ix) $-[C(R^{11})_2]_nCN$;

x) $-[C(R^{11})_2]_nCNO$;

xi) $-[C(R^{11})_2]_nCF_3$, $-[C(R^{11})_2]_nCCl_3$, $-[C(R^{11})_2]_nCBr_3$;

xii) $-[C(R^{11})_2]_nN(R^4)_2$;

xiii) $-[C(R^{11})_2]_nNR^4COR^4$;

xiv) $-[C(R^{11})_2]_nNR^4CN$;

xv) $-[C(R^{11})_2]_nNR^4C(=NR^4)N(R^4)_2$;

xvi) $-[C(R^{11})_2]_nNHN(R^4)_2$;

xvii) $-[C(R^{11})_2]_nNHOR^4$;

xviii) $-[C(R^{11})_2]_nNCS$;

xix) $-[C(R^{11})_2]_nNO_2$;

xx) $-[C(R^{11})_2]_nOR^4$;

xxi) $-[C(R^{11})_2]_nOCN$;

xxii) $-[C(R^{11})_2]_nOCF_3$, $-[C(R^{11})_2]_nOCCl_3$, $-[C(R^{11})_2]_nOCBr_3$;

xxiii) F, Cl, Br, I, and mixtures thereof;

xxiv) $-[C(R^{11})_2]_nSO_3M$;

xxv) $-[C(R^{11})_2]_nOSO_3M$;

xxvi) $-[C(R^{11})_2]_nSCN$;

xxvii) $-[C(R^{11})_2]_nSO_2N(R^4)_2$;

xxviii) $-[C(R^{11})_2]_nSO_2R^4$;

xxix) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;

xxx) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;

xxxi) haloalkyl having the formula $-[C(R^9)_2]_nC(R^9)_3$;

xxxii) and mixtures thereof;

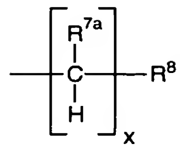
R^4 is the same as defined herein above; R^9 is R^4, fluorine, chlorine, bromine, iodine, and mixtures thereof; each R^{11} is hydrogen or R^{10}; the index n has the value from 0 to 10.

R^8 is selected from the group consisting of:

i) hydrogen;
ii) C_3-C_8 non-aromatic carbocyclic rings;
iii) C_6-C_{14} aromatic carbocyclic rings;
iv) C_1-C_7 non-aromatic heterocyclic rings;
v) C_3-C_{13} aromatic heterocyclic rings;
vi) $-C(Y)R^4$;
vii) $-C(Y)_2R^4$;
viii) $-C(Y)N(R^4)_2$;
ix) $-C(Y)NR^4N(R^4)_2$;
x) -CN;
xi) -CNO;
xii) $-[C(R^9)_2]C(R^9)_2$;
xiii) $-N(R^4)_2$;
xiv) $-NR^4CN$;
xv) $-NR^4C(Y)R^4$;
xvi) $-NR^4C(Y)N(R^4)_2$;
xvii) $-NHN(R^4)_2$;
xviii) $-NHOR^4$;
xix) -NCS;
xx) $-NO_2$;
xxi) $-OR^4$;
xxii) -OCN;
xxiii) $-OCF_3$, $-OCCl_3$, $-OCBr_3$;
xxiv) -F, -Cl, -Br, -I, and mixtures thereof;
xxv) -SCN;
xxvi) $-SO_3M$;
xxvii) $-OSO_3M$;
xxviii) $-SO_2N(R^4)_2$;
xxix) $-SO_2R^4$;
xxx) $-[C(R^{11})_2]_nP(O)(OR^4)R^4$;
xxxi) $-[C(R^{11})_2]_nP(O)(OR^4)_2$;
xxxii) and mixtures thereof;

wherein R^4, M, Y, and the index x are the same as defined herein above.

The first aspect of W^1 relates to units having the formula:



wherein R^8 is a unit selected from the group consisting of:

a) C_6-C_{14} aromatic carbocyclic rings: (group (iii) above); or

b) C_3-C_{13} aromatic heterocyclic rings: (group (v) above);

and R^{7a} is selected from the group consisting of:

a) hydrogen;

b) $-COR^4$;

c) $-COOR^4$;

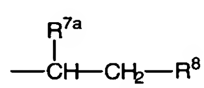
d) $-CON(R^4)_2$; and

e) $-N(R^4)_2$;

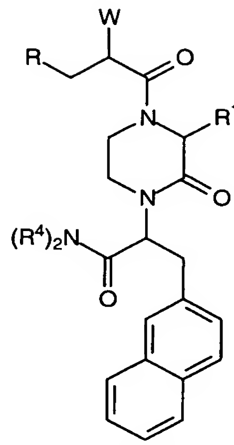
wherein for this aspect of R^8 each R^4 is independently hydrogen, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, methoxy, and mixtures thereof. The index x is equal to 1 or 2.

R^8 units which are suitable for use in this aspect of W^1 include units selected from the group consisting of (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, (2,3-difluorophenyl)methyl, (2,4-difluorophenyl)methyl, (3,4-difluorophenyl)methyl, (3,5-difluorophenyl)-methyl, (2-chlorophenyl)methyl, (3-chlorophenyl)methyl, (4-chlorophenyl)methyl, (2,3-dichlorophenyl)methyl, (2,4-dichlorophenyl)methyl, (3,4-dichlorophenyl)methyl, (3,5-dichlorophenyl)-methyl, and naphthalene-2-ylmethyl.

Iterations of this aspect of the present invention relate to units having the formula:



and encompass scaffolds wherein R^{7a} is an amide, for example, compounds having the following formulae:



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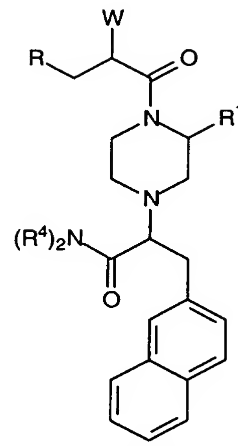
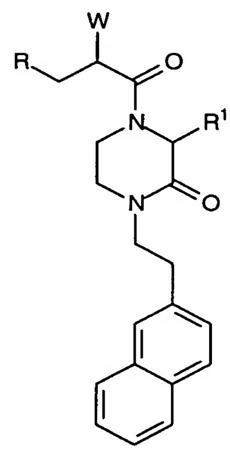


and to scaffolds wherein R^{7a} and R^{7b} are each hydrogen, for example:



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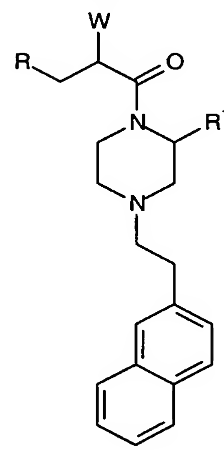


The second aspect of W^1 units comprise R^{7a} units which are short chain alkyl or alkenyl (lower hydrocarbyl) esters having the formula:

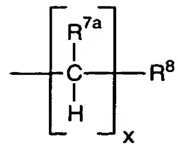
$$-C(O)OR^4;$$

non-limiting examples of which are $-C(O)OCH_3$; $-C(O)OCH_2CH_3$; $-C(O)OCH_2CH_2CH_3$; $-C(O)OCH_2CH_2CH_2CH_3$; $-C(O)OCH(CH_3)_2$; $-C(O)OCH_2CH(CH_3)_2$; $-C(O)OCH_2CH{=}CHCH_3$; $-C(O)OCH_2CH_2CH(CH_3)_2$; $-C(O)OCH_2C(CH_3)_3$; and the like; and short chain substituted or non-substituted amides having the formula:

$$-C(O)NHR^4 \text{ or } -NHC(O)R^4$$

non-limiting examples of which are $-C(O)NHCH_3$; $-C(O)NHCH_2CH_3$; $-C(O)NHCH(CH_3)_2$; $-C(O)NHCH_2CH_2CH_3$; $-C(O)NHCH_2CH_2CH_2CH_3$; $-C(O)NHCH_2CH(CH_3)_2$; $-C(O)NH_2$; $-C(O)NHCH_2CH{=}CHCH_3$; $-C(O)NHCH_2CH_2CH(CH_3)_2$; $-C(O)NHCH_2C(CH_3)_3$; $-C(O)NHCH_2CH_2SCH_3$; $-C(O)NHCH_2CH_2OH$; $-NHC(O)CH_3$; $-NHC(O)CH_2CH_3$; $-NHC(O)-CH_2CH_2CH_3$; and the like.

The third aspect of W^1 units comprise units which are guanidine and guanidine mimetics having the formula:



and R^{7a} is a unit selected from the group consisting of:

a) $-C(Y)N(R^{12})_2$;

b) $-C(Y)NR^{12}N(R^{13})_2$;

c) $-NR^{12}C(Y)N(R^{13})_2$; and

d) $-NHN(R^{12})_2$;

wherein Y is =O, =S, $=NR^{14}$, and mixtures thereof, R^{12}, R^{13} and R^{14} are each independently hydrogen, methyl, cyano, hydroxy, nitro, and mixtures thereof; the index x is from 0 to 5; and R^8 is selected from the group consisting of benzyl, (2-chlorophenyl)methyl, (3-chlorophenyl)-methyl, (4-chlorophenyl)methyl, (3,4-dichlorophenyl)methyl, (2-fluorophenyl)-methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, and naphthalen-2-ylmethyl.

Another iteration of this aspect relates to W^1 units wherein R^{7a} is selected from the group consisting of:

i) hydrogen;

ii) $-CO_2H$;

iii) $- CO_2CH_3$;

iv) $-CONH_2$;

v) $-CONHCH_3$;

vi) $-CON(CH_3)_2$;

vii) $-CONH(CH_2CH_2F)$;

viii) $-CONCH(CH_3)_2$;

ix) $-CONH(C_3H_5)$;

x) $-CONHCH_2(C_3H_5)$;

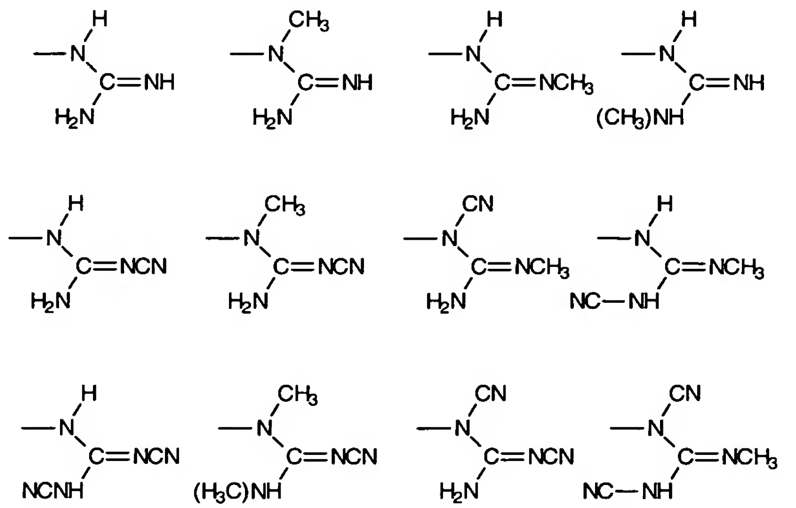
and R^8 is selected from the group consisting of benzyl, (2-chlorophenyl)methyl, (3-chlorophenyl-)methyl, (4-chlorophenyl)methyl, (3,4-dichlorophenyl)methyl, (2-fluorophenyl)-methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, and naphthalen-2-ylmethyl.

A further aspect of W^1 relates to A, A^1, or A^2 units which comprise a $-NR^6-$ unit and R^6 has the formula $-CH_2R^8$ wherein R^8 is selected from the group consisting of phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, and naphth-2-yl.

Non-limiting examples of W^1 wherein R^{7a} units have the formula:

$$-NR^{12}C(NR^{14})N(R^{13})_2;$$

are selected from the group consisting of:

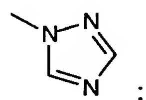


The fourth aspect of the present invention as it relates to W^1 units are the 5-member ring W^1 units having the formula:

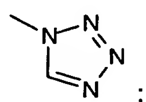
$$—(CH_2)_x—R^8$$

wherein the index x is 0, 1, 2, or 3 and R^8 is selected from the group consisting of:

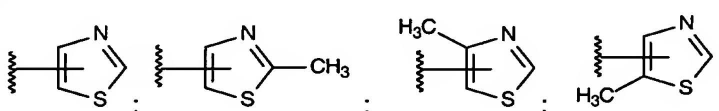
i) triazolyl having the formula:



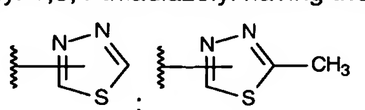
ii) tetrazolyl having the formula:



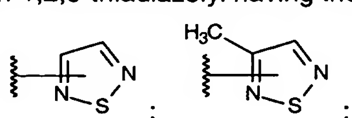
iii) thiazolyl, 2-methylthiazolyl, 4-mentylthiazolyl, 5-methylthiazolyl having the formula:



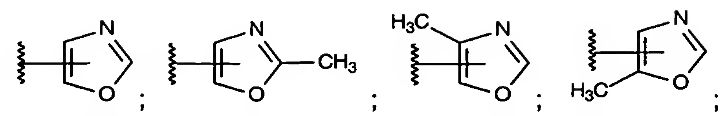
iv) 1,3,4-thiadiazolyl, 2-methyl-1,3,4-thiadiazolyl having the formula:



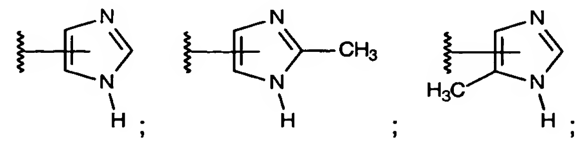
v) 1,2,5-thiadiazolyl, 3-methyl-1,2,5-thiadiazolyl having the formula:



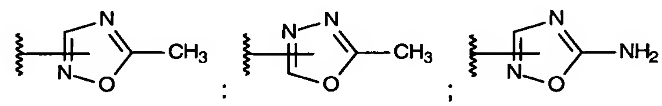
vi) oxazolyl, 2-methyloxazolyl, 4-methyloxazolyl, 5-methyloxazolyl having the formula:



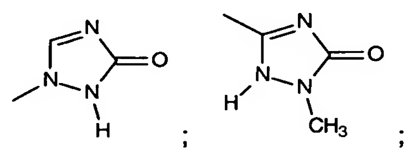
vii) imidazolyl, 2-methylimidazolyl, 5-methylimidazolyl having the formula:



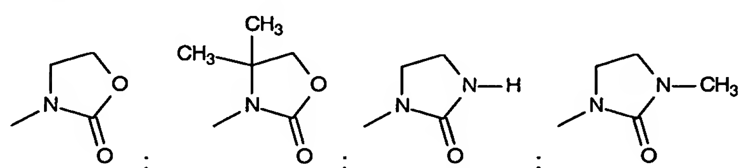
viii) 5-methyl-1,2,4-oxadiazolyl, 2-methyl-1,3,4-oxadiazolyl, 5-amino-1,2,4-oxadiazolyl, having the formula:



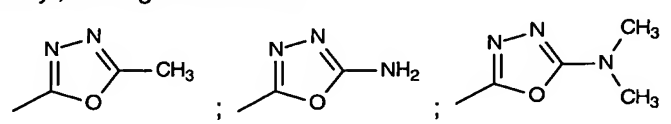
ix) 1,2-dihydro[1,2,4]triazol-3-one-1-yl, 2-methyl-1,2-dihydro[1,2,4]triazol-3-one-5-yl, having the formula:



x) oxazolidin-2-one-3-yl; 4,4-dimethyloxazolidin-2-one-3-yl; imidazolidin-2-one-1-yl; 1-methylimidazolidin-2-one-1-yl, having the formula:

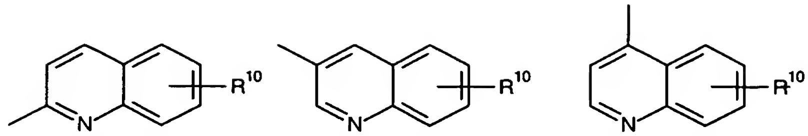


xi) 2-methyl-1,3,4-oxadiazolyl, 2-amino-1,3,4-oxadiazolyl, 2-(N,N-dimethylamino) - 1,3,4-oxadiazolyl, having the formula:

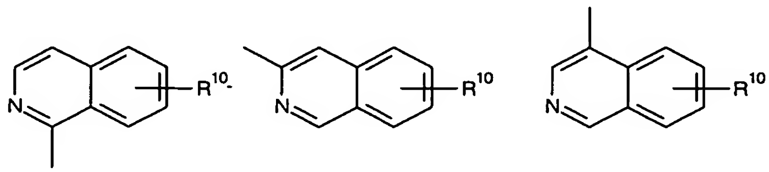


A fourth aspect of W^1 of this first category of receptor ligands relates to R^5 units comprising substituted an unsubstituted, saturated and unsaturated six-member rings having at least one nitrogen, non limiting examples of which include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, morpholinyl, and the like.

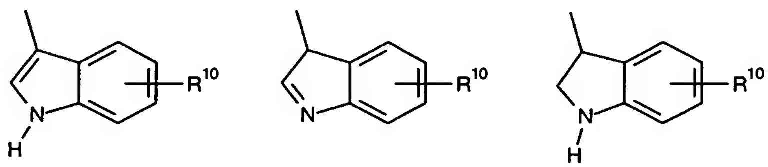
A fifth aspect of W^1 of this first category of receptor ligands relates to R^5 units comprising substituted and unsubstituted fused ring heterocycles for example, quinolin-2-yl, quinolin-3-yl, and quinolin-4-yl units having the formula:



substituted and unsubstituted isoquinolin-1-yl, isoquinolin-3-yl, and 1soquinolin-4-yl units having the formula:

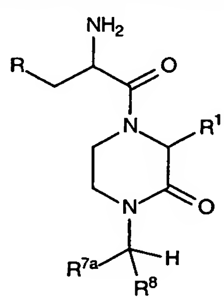


and unsubstituted [5,6] fused ring systems, *inter alia*, 1*H*-indolin-3-yl having the formula:



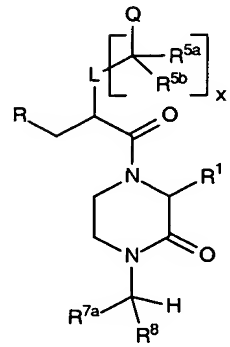
The analogs (compounds) of the present invention are arranged into several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein. The melanocortin receptor ligands of the present invention are differentiated into categories depending upon the ring A unit selections. However, preparation strategies and synthetic routes suitable for one ring scaffold may be suitable or adaptable to other ring systems or ring substituents.

Non-limiting examples of categories of the present invention include Category I analogs comprising a 2-oxo-3-hydrocarbyl-piperazines the first aspect of which has the formula:



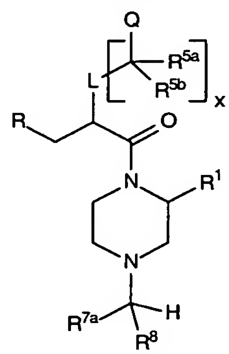
;

Category II analogs comprise a 2-oxo-3-hydrocarbyl-piperazine having the formula:



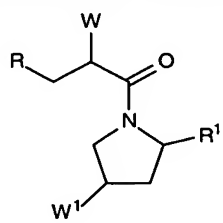
;

Category III relates to 3-hydrocarbyl-piperazines having the formula:



;

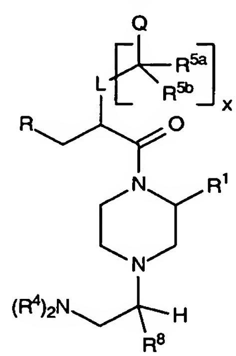
Category IV comprises 2-hydrocarbyl-pyrrolidines having the formula:



.

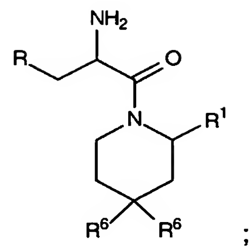
Other non-limiting examples of scaffolds according to the present invention include:

2-hydrocarbyl-4-β-aminohydrocarbyl-piperazine having the formula:

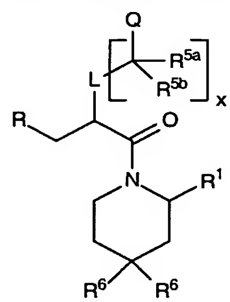


;

2-hydrocarbyl-4,4-disubstituted-piperidine having the formula:

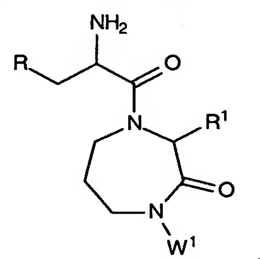


2-hydrocarbyl-4,4-disubstituted-piperidine having the formula:

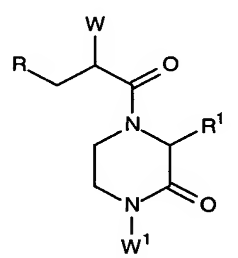


; and

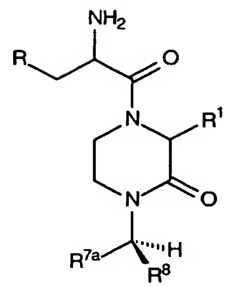
2-oxo-3-hydrocarbyl-[1,4]diazepane having the formula:



Category I melanocortin receptor ligands according to the present invention comprise the 2-oxo-3-hydrocarbyl-piperazines having the general scaffold with the formula:



The first aspect of Category I comprises analogs wherein W is $-NH_2$, said analogs having a scaffold with the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{7a} and R^8 are provided herein below in Table I.

TABLE I

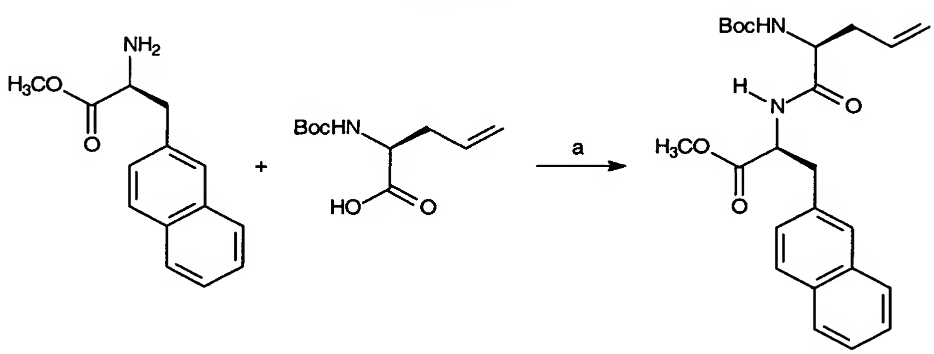
No.	R^1	R^{7a}	R^8
1	methyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
2	ethyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
3	propyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
4	*iso*-propyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
5	butyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
6	cyclopropyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
7	cyclopropylmethyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
8	allyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
9	but-2-enyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
10	propargyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
11	methyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
12	ethyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
13	propyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
14	*iso*-propyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
15	butyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
16	cyclopropyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
17	cyclopropylmethyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
18	allyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
19	but-2-enyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
20	propargyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
21	methyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
22	ethyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
23	propyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
24	*iso*-propyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
25	butyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl

26	cyclopropyl	-C(O)N(CH_3)$_2$	naphthylen-2-ylmethyl
27	cyclopropylmethyl	-C(O)N(CH_3)$_2$	naphthylen-2-ylmethyl
28	allyl	-C(O)N(CH_3)$_2$	naphthylen-2-ylmethyl
29	but-2-enyl	-C(O)N(CH_3)$_2$	naphthylen-2-ylmethyl
30	propargyl	-C(O)N(CH_3)$_2$	naphthylen-2-ylmethyl
31	methyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
32	ethyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
33	propyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
34	*iso*-propyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
35	butyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
36	cyclopropyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
37	cyclopropylmethyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
38	allyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
39	but-2-enyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
40	propargyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
41	methyl	-C(O)NH_2	(4-chlorophenyl)methyl
42	ethyl	-C(O)NH_2	(4-chlorophenyl)methyl
43	propyl	-C(O)NH_2	(4-chlorophenyl)methyl
44	*iso*-propyl	-C(O)NH_2	(4-chlorophenyl)methyl
45	butyl	-C(O)NH_2	(4-chlorophenyl)methyl
46	cyclopropyl	-C(O)NH_2	(4-chlorophenyl)methyl
47	cyclopropylmethyl	-C(O)NH_2	(4-chlorophenyl)methyl
48	allyl	-C(O)NH_2	(4-chlorophenyl)methyl
49	but-2-enyl	-C(O)NH_2	(4-chlorophenyl)methyl
50	propargyl	-C(O)NH_2	(4-chlorophenyl)methyl
51	methyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
52	ethyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
53	propyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
54	*iso*-propyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
55	butyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
56	cyclopropyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
57	cyclopropylmethyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
58	allyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
59	but-2-enyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
60	propargyl	-C(O)$NHCH_3$	(4-chlorophenyl)methyl
61	methyl	-C(O)N(CH_3)$_2$	(4-chlorophenyl)methyl

62	ethyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
63	propyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
64	*iso*-propyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
65	butyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
66	cyclopropyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
67	cyclopropylmethyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
68	allyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
69	but-2-enyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
70	propargyl	-C(O)N(CH3)2	(4-chlorophenyl)methyl
71	methyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
72	ethyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
73	propyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
74	*iso*-propyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
75	butyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
76	cyclopropyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
77	cyclopropylmethyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
78	allyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
79	but-2-enyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl
80	propargyl	-C(O)NH(CH2CH2F)	(4-chlorophenyl)methyl

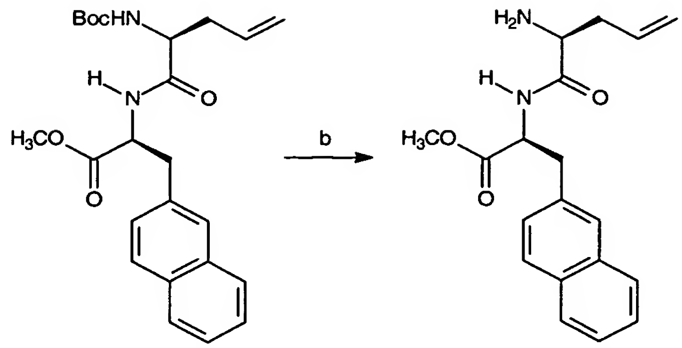
The compounds of the first aspect of Category I can be suitably prepared by the procedure outlined herein below in Scheme I.

Scheme I



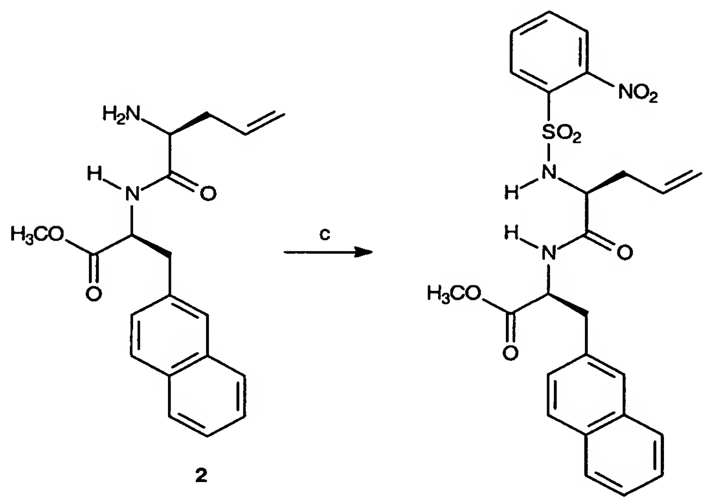
1

Reagents and conditions: (a) EDCI, HOBt, NMM; rt, 3 hr.



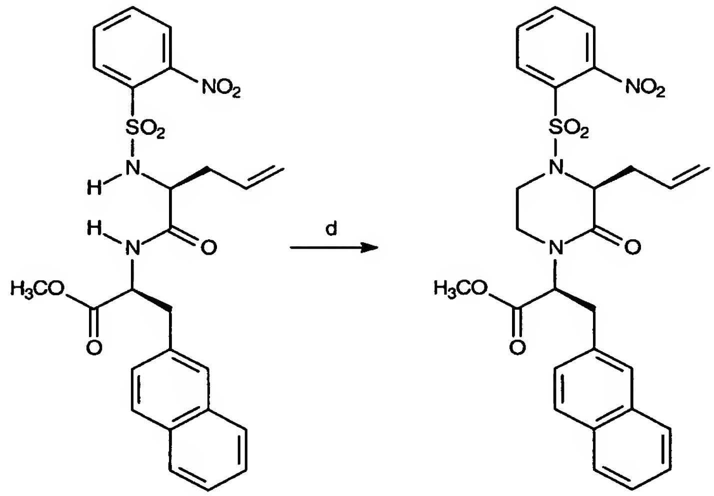
1 2

Reagents and conditions: (b) TFA; rt, 3 hr.



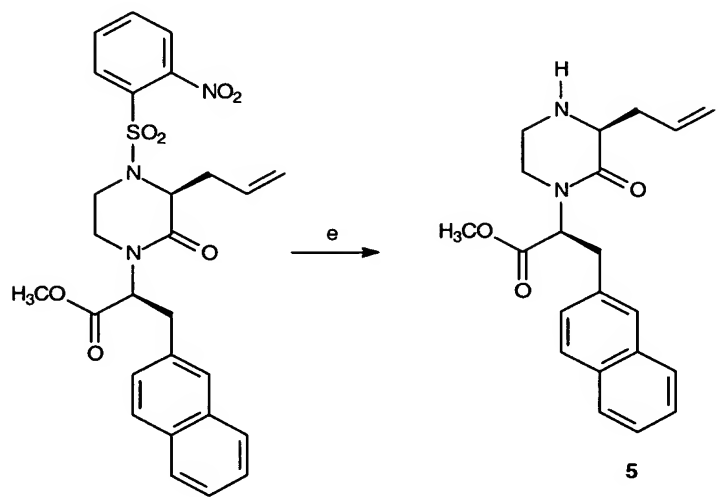
2 3

Reagents and conditions: (c) 2-nitrophenylsulfonyl cloride, Et_3N; rt, 10 hr.



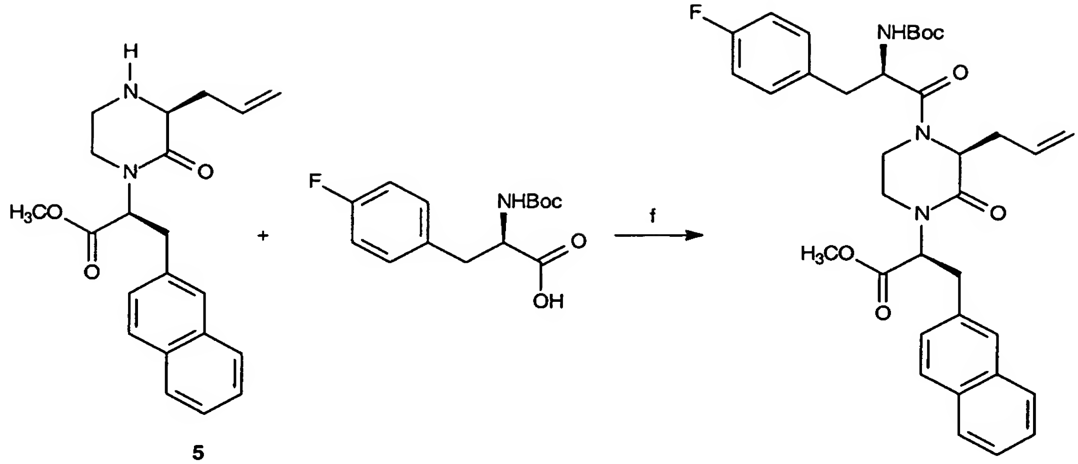
3 4

Reagents and conditions: (d) 1,2-dibromoethane, K_2CO_3, DMF; 65 °C, 12 hr.



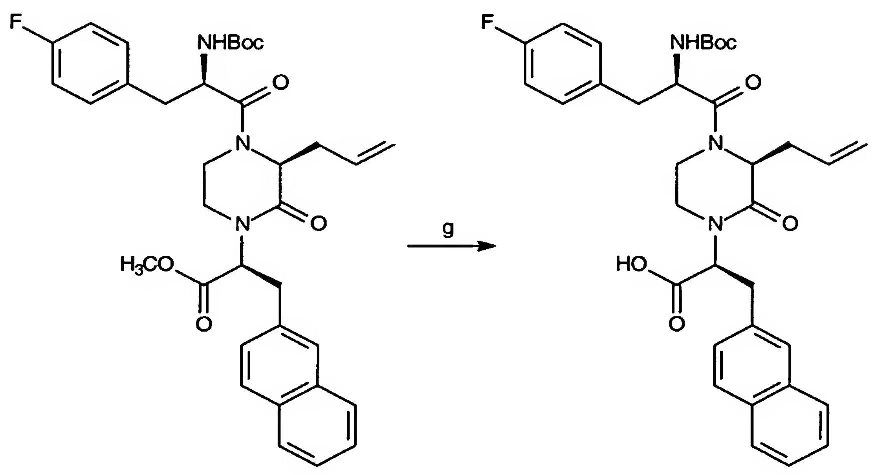
4 5

Reagents and conditions: (e) 4-mercaptophenol, K_2CO_3, DMF; rt, 18 hr.



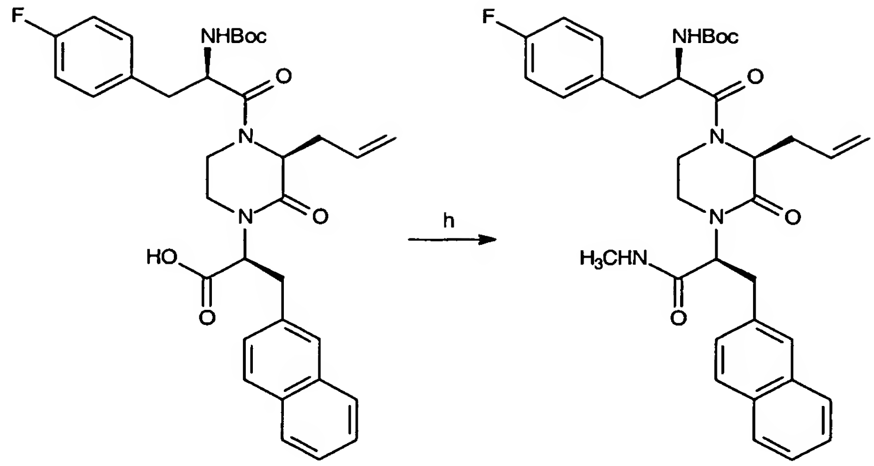
5 6

Reagents and conditions: (f) PyBOP, TEA, CH_2Cl_2; rt, 20 hr.



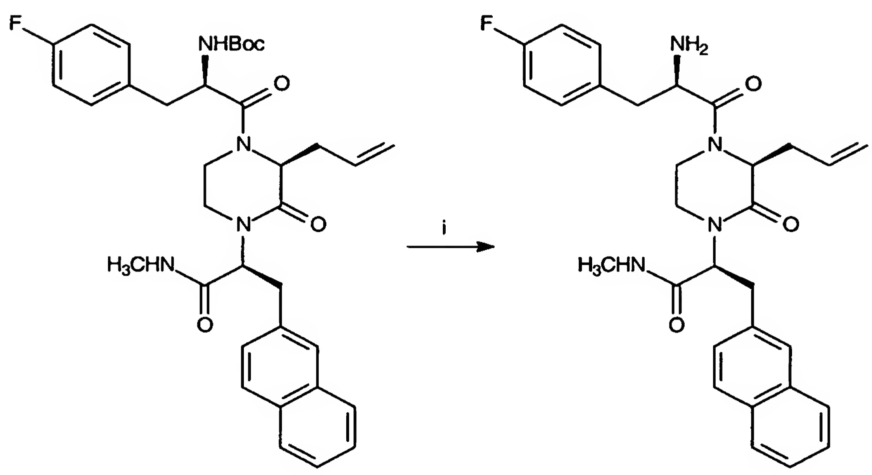
6 7

Reagents and conditions: (g) LiOH, THF/MeOH/H_2O; rt, 3 hr.



7 8

Reagents and conditions: (h) NH_2CH_3, EDCI, HOBt, NMM, DMF; rt, 18 hr.



8 9

Reagents and conditions: (i) TFA, CH_2Cl_2; rt, 45 min.

EXAMPLE 1

2-{3-Allyl-4-[2-amino-3-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (9)

Preparation of (*S,S*)-2-(2-*tert*-butoxycarbonylamino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic acid methyl ester (1): To a solution of 2-(*S*)-*tert*-butoxycarbonylamino-pent-4-enoic acid (3.8g, 18.0 mmol) and 2-(*S*)-amino-3-naphthalen-2-yl-propionic acid methyl ester (4.1g, 18.0 mmol) in DMF (40 mL) are added 1-hydroxybenzotriazole (3.1g, 23.4 mmol), N-methylmorpholine (9.1g, 90.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (4.5 g, 23.4 mmol) consecutively and the reaction mixture is stirred for 3 hours.

The reaction is quenched with aqueous NH_4Cl and extracted with ethyl acetate. The extract is dried over Na_2SO_4, filtered and concentrated in vacuo and the residue purified over silica gel (hexanes/ethyl acetate, 1:1) to afford 6.4 g (84% yield) of the desired product.

Preparation of (*S,S*)-2-(2-amino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic acid methyl ester (2): To a solution of (*S,S*)-2-(2-*tert*-butoxycarbonylamino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic acid methyl ester, **1**, (6.2g, 14.64 mmol) in methylene chloride (40 mL) is added trifluoroacetic acid (5 mL). The reaction mixture is stirred for 3 hours and the solvent and excess trifluoroacetic acid are removed under in vacuo. The residue is dried under high vacuum for several hours and 6.35 g of the crude trifluoroacetate salt of the desired product is obtained, which is used without further purification.

Preparation of (*S,S*)-3-naphthalen-2-yl-2-[2-(2-nitro-benzenesulfonylamino)-pent-4-enoylamino]-propionic acid methyl ester (3): To a solution of (*S,S*)-2-(2-amino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic acid methyl ester salt, **2**, (4.2g) in $CHCl_3$ (50 mL) are added triethyl amine (3.8g, 38 mmol) and 2-nitrophenylsulfonyl chloride (2.5g, 11.5 mmol). The reaction is stirred for 10 hours then quenched with 10% aqueous HCl. The solvent is decanted, and the aqueous phase is extracted with ethyl acetate, the organic layers combined, dried and concentrated in vacuo to afford a crude residue which is purified over silica (hexanes/EtOAc, 3:2) to afford 3.84 g of the desired product.

Preparation of (*S,S*)-2-[3-Allyl-4-(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester (4): To a solution of (*S,S*)-3-naphthalen-2-yl-2-[2-(2-nitro-benzenesulfonylamino)-pent-4-enoylamino]-propionic acid methyl ester, **3**, (3.6 g, 7.0 mmol) and 1,2-dibromoethane (13.2 g, 70.0 mmol) in DMF (40 mL) is added potassium carbonate (9.6 g, 70.0 mmol). The reaction suspension was stirred at 65 °C for 12h, quenched with 10% aqueous HCl and extracted with EtOAc. The extract is dried over Na_2SO_4, concentrated and the residue purified over silica gel (hexanes/EtOAc,1:2) to afford 3.7g (97% yield) of the desired product.

Preparation of (*S,S*)-2-(3-allyl-2-oxo-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester (5): To a solution of (*S,S*)-2-[3-allyl-4-(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester, **4**, (4.8 g, 8.9 mmol) and 4-mercaptophenol (4.5 g, 35.7 mmol) in DMF (35 mL) is added potassium carbonate (7.4 g, 53.4 mmol). The reaction mixture is stirred 18 hours then quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (200 mL). The extract is dried over Na_2SO_4 and concentrated *in vacuo* to afford a bright yellow oil which is purified over silica gel (hexanes/EtOAc, 1:1 to EtOAc/MeOH, 10:1) to afford 2.45 g (79% yield) of the desired product.

Preparation of (*S*)-2-{3-(*S*)-allyl-4-[2-(*R*)-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (6): To a solution of (*S,S*)-2-(3-allyl-2-oxo-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester, **5**, (500 mg, 1.42 mmol) in CH_2Cl_2 (5.0 mL) are added 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-fluorophenyl)propionic acid (473 mg, 1.67 mmol), benzotriazole-1-yl-oxy-tris-pyrrolidinol-phosphonium hexafluorophosphate (PyBOP) (960 mg, 1.85 mmol) and triethylamine (169 mg, 1.67 mmol). The reaction mixture is stirred for 20 h, quenched with 10% $NaHCO_3$ aqueous solution and extracted with EtOAc. The extract is dried over Na_2SO_4, filtered and concentrated. The residue is purified over silica gel (hexanes/ethyl acetate, 4:1 to 3:2) to afford 0.745 g (85% yield) of the desired product.

Preparation of (*S*)-2-{3-(*S*)-Allyl-4-[2-*tert*-butoxycarbonylamino-3-(*R*)-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (7): To a solution of (*S*)-2-{3-(*S*)-allyl-4-[2-(*R*)-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **6**, (200 mg, 0.324 mmol) in a mixture of THF (1mL)/CH_3OH (0.5 mL)/H_2O (0.5 mL) is added LiOH (43 mg, 1.78 mmol). The reaction mixture is stirred for 3 hours, acidified with 1N HCl to pH 3 and extracted with EtOAc. The extract is dried over Na_2SO_4, filtered, concentrated and dried under high vacuum to afford the desired product in quantitative yield, which is used without further purification.

Preparation of (2-(*R*)-{2-(*S*)-allyl-4-[1-(*S*)-(methylcarbamoyl-2-naphthalen-2-ylethyl)]-3-oxo-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (8): To a solution of (*S*)-2-{3-(*S*)-allyl-4-[2-*tert*-butoxycarbonylamino-3-(*R*)-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid, **7**, (195 mg) in DMF (3 mL) are added methylamine (2M, 0.175 mL, 0.35 mmol), 1-hydroxybenzotriazole (57 mg, 0.42 mmol), N-methylmorpholine (162 mg, 1.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (80 mg, 0.42 mmol) consecutively and the reaction mixture is stirred 18 hours. The reaction is then quenched with aqueous NH_4Cl and extracted with ethyl acetate. The extract is dried over Na_2SO_4, filtered and concentrated *in vacuo* and the resulting residue is purified over silica gel (hexanes/ethyl acetate, 1:1) to afford 0.183 g (88% yield) of the desired product.

Preparation of 2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (9): To a solution of (2-(*R*)-{2-(*S*)-allyl-4-[1-(*S*)-(methylcarbamoyl-2-naphthalen-2-ylethyl)]-3-oxo-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl)-carbamic acid *tert*-butyl ester, **8**, (32 mg, 0.052 mmol) in CH_2Cl_2 (1 mL) is added trifluoroacetic acid. The reaction mixture is stirred for 45 min, concentrated *in vacuo* and the

resulting residue purified by reverse phase HPLC to afford 27 mg of the trifluoroacetate salt of the desired product.

In the above example for the preparation of analogs encompassed by the first aspect of Category I, 2-(*S*)-*tert*-butoxycarbonylamino-pent-4-enoic acid is used for the preparation of compound **1**. Other analogs encompassed within the first aspect of Category I wherein R^1 comprises other units as defined herein above, can be prepared by substituting the appropriate starting material in place of 2-(*S*)-*tert*-butoxycarbonylamino-pent-4-enoic acid, for example, 2-(*S*)-*tert*-butoxycarbonylamino-propionic acid, 2-(*S*)-*tert*-butoxycarbonylamino-butyric acid, 2-(*S*)-*tert*-butoxycarbonylamino-pentanoic acid, 2-(*S*)-*tert*-butoxycarbonylamino-3-methyl-butyric acid, 2-(*S*)-*tert*-butoxycarbonylamino-3-cyclopropyl-propionic acid, and the like. The formulator may also choose to prepare rings which comprise the opposite stereochemistry, for example, those derived from the use of 2-(*R*)-*tert*-butoxy-carbonylamino-pent-4-enoic acid or, as a further iteration, the formulator may wish to provide a racemic mixture, for example, an analog derived from 2-(*R,S*)-*tert*-butoxycarbonylamino-pent-4-enoic acid.

As described herein above and as exemplified in both Table I and Scheme I, the formulator may choose to substitute for naphthylen-2-ylmethyl (R^8 units). Non-limiting examples of suitable groups include benzyl, 3-methoxybenzyl, 4-methoxybenzyl, 3-benzo[1,3]dioxol-5-ylmethyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2,4-difluorobenzyl, 3,5-difluorobenzyl, 3,4-difluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-phenylbenzyl, isoquinolin-6-yl, indol-2-yl, indol-3-yl, and the like.

In addition, the R^{7a} unit may include, for example, $-CH_2C(O)NH_2$, $-CH_2C(O)N(CH_3)_2$, $-C(O)N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NH(CH_2CH_2F)$, $-C(O)NHCH_2(C_3H_5)$, and the like.

In addition, R units can be modified to reflect the choice of the formulator, for example, 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-fluorophenyl)propionic acid can be replaced by 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-chlorophenyl)propionic acid to replace the 4-fluorophenyl R unit with the 4-chlorophenyl R unit. Non-limiting examples of other suitable replacements include 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(3-fluorophenyl)propionic acid, 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(2,4-difluorophenyl)propionic acid, 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-methylphenyl)propionic acid, 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-hydroxyphenyl)propionic acid, 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-trifluoromethylphenyl)propionic acid, and the like.

These changes and iterations can be made by replacement of one or more reagents or starting materials described herein above in Scheme I.

The following are non-limiting examples of compounds which comprise the first aspect of Category I analogs.

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methyl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 8.02-8.22 (m, 0.4H), 6.95-7.50 (m, 7H), 5.52 (dd, J = 11.5, 5.2 Hz, 0.75H), 5.41 (dd, J = 10.8, 6.3 Hz, 0.25H), 4.02-4.76 (m, 1.3H), 4.28-4.46 (m, 0.7H), 3.40-3.74 (m, 2H), 2.66 3.30 (m, 9H), 1.12-1.44 (m, 2H), 0.86-1.08 m, 0.6H), 0.75-0.85 (m, 4.4H); MS (ESMS) *m/z* 537.2, 539.2, 541.2 $(M+H)^+$, Cl_2 isotope pattern.

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-(2-fluoroethyl)-3-naphthalen-2-yl-propionamide: MS (ESMS) *m/z* 563.5 $(M+H)^+$.

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90~7.90 (m, 11H), 5.30~5.60 (m, 1H), 2.60~4.00 (m, 13H), 0.80~1.60 (m, 2H), -0.49~0.2 (m, 5H); MS (ES-MS) *m/z* 531 (M+1).

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00~8.00 (m, 11H), 4.57 (m, 1H), 4.10~4.30 (m, 2H), 2.60~3.75 (m, 12H), 1.85 (bs, 2H), 1.25~1.50 (m, 2H), 0.40~0.60 (m, 3H); MS (ES-MS) *m/z* 592 (M+1).

3-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-methyl-4-naphthalen-2-yl-butyramide. ^{1}H NMR (CDCl3, 300 MHz) 6.80~7.80 (m, 11H), 2.40~3.60 (m, 16H), 0.92 (m, 2H), 0.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 mHz) 172.01, 168. 22, 167.37, 134.53, 133.59, 132.64, 131.56, 131.47, 129.46, 128.50, 127.94, 127.54, 127.16, 126.15, 116.18, 115.89, 56.38, 51.07, 41.18, 39.00, 38.46, 37.87, 37.27, 34.33, 31.22, 26.58, 18.80, 13.55; MS (ES-MS) m/z 533 (M+1).

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.00~8.00 (m, 11H), 4.57 (m, 1H), 4.10~4.30 (m, 2H), 2.60~3.75 (m, 12H), 1.85 (bs, 2H), 1.25~1.50 (m, 2H), 0.40~0.60 (m, 3H); MS (ES-MS) *m/z* 592 (M+1).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.85-7.54, (m, 4H); 7.54-7.37, (m, 3H); 7.28-7.17, (m, 2H); 7.07-6.96, (m, 2H); 4.67-4.55, (m, 1H); 3.65-2.93, (m, 10H); 2.86-2.69, (m, 4H); 1.89-1.84, (m, 2H), 1.04-0.78, (m, 2H); 0.63-0.26, (m, 4H). ^{13}C NMR (CD_3OD, 300 MHz) δ 171.02, 170.91, 168.77, 167.03, 167.00, 164.32, 161.06, 134.27, 133.73,

132,.80, 131.52, 131.41, 131.06, 129.93, 128.12, 127.60, 127.49, 127.32, 127.02, 126.24, 125.71, 115.76,115.48, 56.28, 56.15, 50.71, 46.25, 46.17, 41.49, 41.32, 36.60, 34.41, 34.23, 26.26, 26.14, 25.26, 18.41, 18.38, 12.58. MS(ESI) m/e 519 [M+1].

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-(2-fluoroethyl)-3-naphthalen-2-yl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.84-7.68, m, 4H; 7.50-7.31, m, 5H; 7.15-7.08, m, 2H; 4.77-4.57, m, 2H; 4.42-4.34, m, 1H; 4.27-4.17, m, 1H; 4.11-4.05, m, .5H; 3.82-2.79, m, 11H; 2.59-2.52, m, 0.5H; 1.77-1.30, m, 2.5H; 1.21-1.13, m, 2H; 0.85-0.83, t, (J=7.13Hz), 3H; ^{13}C NMR (CD_3OD, 300 MHz) δ 170.76, 169.75, 169.54, 134.16, 133.80, 132.78, 132.65,132.32, 131.76, 131.59, 130.02,127.99, 127.49, 126.06, 125.65, 115.84, 115.71, 115.55, 82.86, 82.73, 69.53, 69.25, 52.75, 50.88, 50.43, 49.44, 40.36, 39.69, 39.44, 36.63, 34.12, 33..87, 31.89, 31.02, 19.19,19.02, 12.95, 12.85. MS(ESI) m/e 536 [M+1].

2-{4-[2-Amino-3R-(4-fluorophenyl)-propionyl]-2-oxo-3S-propyl-piperazin-1-yl}-N-methyl-3S-thiazol-4-yl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.94 (d, H, J=1.52 Hz) 7.49-7.41 (m, 3H) 7.28-7.08 (m, 2H) 7.01 (t, 1H, J=8.71 Hz) 5.52 (q, 1H, J=6.95 Hz) 4.76 (t, 1H, J=6.69 Hz) 4.68 (t, 1H, J=7.60 Hz) 3.76-3.64 (m, 2H) 3.62-3.46 (m, 2H) 3.17-3.01 (m, 4H) 2.74 (s, 3H) 1.54-29 (m, 2H) 1.08-0.91 (m, 2H) 0.85 (t, 3H, J=7.58 Hz) MS (ESI) m/z 475 ($M+H^+$, 100).

2-{4-[2-Amino-3R-(4-fluorophenyl)-propionyl]-3S-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-isopropyl-3S-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80-7.68 (m, 3H) 7.59-7.55 (m, 1H) 7.49-7.41 (m, 2H) 7.19-7.07 (m, 2H) 6.96 (t, 3H, J=8.38 Hz) 6.42 (d, 1H, J=7.57 Hz) 5.51-5.42 (m, 1H) 3.69-2.78 (m, 11H) 1.18 (d, 2H, J=6.566 Hz) 1.09-1.00 (m, 6H) 0.3-0.1 (m, 5H) MS (ESI) m/z 559 ($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(3,4-dichlorophenyl)-N-isopropyl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.50-6.97 (m, 7H) 5.49-5.38 (m, 1H) 4.63-4.60 (m, 1H) 4.21-4.37 (m, 1H) 4.08-3.85 (m, 1H) 3.74-3.61 (m, 2H) 3.44-2.89 (m, 6H) 1.48-1.09 (m, 10H) 0.93-0.77(m, 3H) MS (ESI) m/z 565 ($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(2-chlorophenyl)-N-isopropyl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.42-6.93 (m, 8H) 5.59-5.43 (m, 1H) 4.73-4.61 (m, 1H) 4.06-3.88 (m, 2H) 3.72-3.53 (M, 4H) 3.42-3.21 (m, 2H) 3.14-2.91 (m, 2H) 1.48-0.74 (m, 13H) MS (ESI) m/z 531 ($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(3-cyano-phenyl)-N-methyl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.67-6.54 (m, 3H)

7.52-7.43 (m, 1H) 7.38-7.18 (m, 2H) 7.16-6.94 (m, 2H) 5.58-5.38 (m, 1H) 4.75-4.60 (m, 1H) 4.38-4.27 (m, 1H) 3.76-3.63 (m, 2H) 3.62-3.43 (m, 2H) 3.20-3.01 (m, 2H) 2.98-2.86 (m, 2H) 2,74 (s, 3H) 1.45-1.14 (m, 4H) 0.93-0.74 (m, 3H) MS (ESI) m/z 494 ($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(3,4-dimethoxy-phenyl)-N-methyl-propionamide: ^1H NMR (CD_3OD, 300 MHz) δ 7.32 (q, 2H, J=1.97 Hz) 7.12 (t, 2H, J=8.74) 6.87-6.71 (m, 3H) 5.51 (q, 1H, J=5.50 Hz) 4.70-4.58 (m, 1H) 3.85-3.76 (m, 6H) 3.68-3.45 (m, 1H) 3.28-2.79 (m, 8H) 2.74 (s, 3H) 1.39-1.06 (m, 4H) 0.86-0.72 (m, 3H) MS (ESI) m/z 529 ($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-isopropyl-3-(S)-p-tolyl-propionamide: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28-6.82(m, 8H) 6.42(d, 1H, J=7.68 Hz) 5.88(d, 1H, J=6.72) 5.39-5.09 (m, 2H) 4.78-4.51(m, 2H) 4.09-3.73 (m, 4H) 3.55-2.60 (m, 6H) 2.52-2.15 (m, 6H) 1.43-0.59 (m, 7H) MS (ESI) m/z 511($M+H^+$, 100).

2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(4-chlorophenyl)-N-ethyl-propionamide: ^1H NMR (CD_3OD, 300 MHz) δ 7.39-6.97 (m, 8H) 5.53-5.35 (m, 2H) 5.02-4.58(m, 4H) 3.71-2.87(m, 10H) 1.50-0.55 (m, 10H) MS (ESI) m/z 517($M+H^+$, 100).

N-Allyl-2-{4-[2-amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-naphthalen-2-yl-propionamide: ^1H NMR (CD_3OD, 300 MHz) δ 7.92-6.92 (m, 11H) 5.98-5.52 (m, 5H) 5.31-5.05 (m, 3H) 4.68-4.42 (m, 2H) 3.92-2.70 (m, 6H) 1.20-0.21 (m, 7H) MS (ESI) m/z 545($M+H^+$, 100).

N-Allyl-2-{4-[2-amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-naphthalen-2-yl-propionamide: ^1H NMR (CD_3OD, 300 MHz) δ 7.98-6.92 (m, 11H) 5.75-5.40 (m, 3H) 5.05-4.00 (m, 2H) 3.82-2.78 (m, 11H) 1.38-0.28 (m, 7H) MS (ESI) m/z 601 ($M+H^+$, 100).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-(2-fluoroethyl)-propionamide trifluoroacetate: ^1H NMR (CD_3OD, with rotamers) δ 7.35-6.85 (m, 8H), 5.52 (m, 1H), 4.69-4.35 (m, 4H), 3.62-2.88 (m, 10H), 1.36-1.17 (m, 2H), 0.84 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.1, 171.9, 170.2, 168.4, 168.1, 164.9, 163.3, 136.9, 136.8, 134.1, 132.9, 132.8, 132.3, 132.3, 132.0, 131.9, 131.3, 131.3, 129.8, 129.8, 117.4, 117.3, 117.1, 116.9, 83.8, 83.7, 82.7, 82.5, 59.3, 57.8, 57.5, 57.4, 52.5, 52.3, 42.9, 42.8,

42.7, 41.3, 41.2, 39.3, 38.3, 37.8, 36.8, 35.8, 35.5, 35.1, 20.0, 19.9, 14.4, 14.3; MS *m/z* (ESI): 535 (M + H, 100), 537 (M + 2 + H, 37).

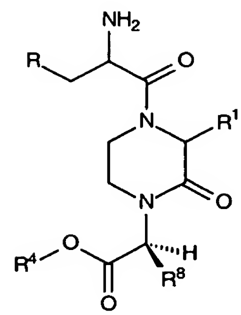
2-{4-[2-Amino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(4-cyano-phenyl)-N-methyl-propionamide: ^{1}H NMR (CD_3OD OD, 300 MHz) δ. 7.71-7.62 (m, 2H) 7.50-7.42 (m, 2H)7.38-7.30 (m, 2H)7.18-7.10 (m, 2H) 5.57-5.41 (m, 1H) 4.71 (t, 1H, J=6.60 Hz) 3.74-3.64 (m, 1H) 3.62-3.46 (m, 4H) 3.18-3.07 (m, 4H) 2.74 (s, 3H) 1.42-1.28 (m, 2H) 1.26-1.13 (m, 2H) 0.81 (s, 3H) MS (ESI) m/z 493 ($M+H^+$, 100).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-(2-fluoroethyl)-3-naphthalen-2-yl-propionamide: ^{1}H NMR (300 MHz, CD_3OD) δ 8.42-8.63 (m, 0.6H), 7.62-7.91 (m, 4H), 7.35-7.60 (m, 3H), 7.13-7.35 (m, 2H), 6.93-7.13 (m, 2H), 5.55-5.80 (m, 1H), 4.16-4.71 (m, 4H), 2.68-3.74 (m, 10H), 0.75-1.11 (m, 2H), 0.18-0.74 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 172.58, 172.48, 170.40, 168.60, 168.33, 165.89, 162.64, 135.76, 135.29, 134.38, 133.08, 132.97, 132.59, 132.48, 131.50, 131.47, 131.02, 129.72, 129.16, 129.06, 128.90, 128.67, 128.54, 127.80, 127.29, 117.33, 117.05, 84.62, 84.50, 82.40, 82.28, 59.46, 57.95, 57.74, 52.65, 52.31, 43.21, 42.97, 41.67, 41.39, 39.46, 38.55, 38.15, 36.79, 36.68, 36.18, 35.83, 19.97, 14.11; MS (ESMS) *m/z* 551.5 $(M+H)^+$.

The following are non-limiting examples of a further iteration of this aspect of Category I wherein R^{7a} is hydrogen:

4-[2-Amino-3-(4-chlorophenyl)-propionyl]-1-(2-naphthalen-2-yl-ethyl)-3-propyl-piperazin-2-one: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.73-7.89 (m, 3H), 7.62 (s, 1H), 7.15-7.55 (m, 7H), 4.68-4.87 (m, 1.3H), 4.32-4.57 (m, 0.7H), 3.92-4.10 (m, 1H), 3.52-3.74 (m, 1H), 3.28-3.51 (m, 1H), 2.74-3.26 (m, 7H), 1.38-1.72 (m, 2H), 0.92-1.37 (m, 2H), 0.74-0.91 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 169.61, 168.62, 168.23, 167.87, 137.74, 137.68, 135.38, 134.32, 134.20, 133.94, 132.80, 132.43, 130.76, 130.54, 129.65, 129.57, 129.15, 128.89, 128.84, 128.76, 127.68, 127.62, 127.05, 59.59, 57.16, 52.04, 51.69, 49.54, 49.31, 47.88, 47.12, 41.66, 39.03, 38.30, 36.21, 35.63, 34.60, 34.39, 20.65, 20.60, 14.63; MS (ESMS) *m/z* 478.3, 480.3 $(M+H)^+$, Cl isotope pattern.

The second aspect of Category I comprises analogs wherein W is $-NH_2$, said analogs having a scaffold with the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^4 and R^8 are described herein below in Table II.

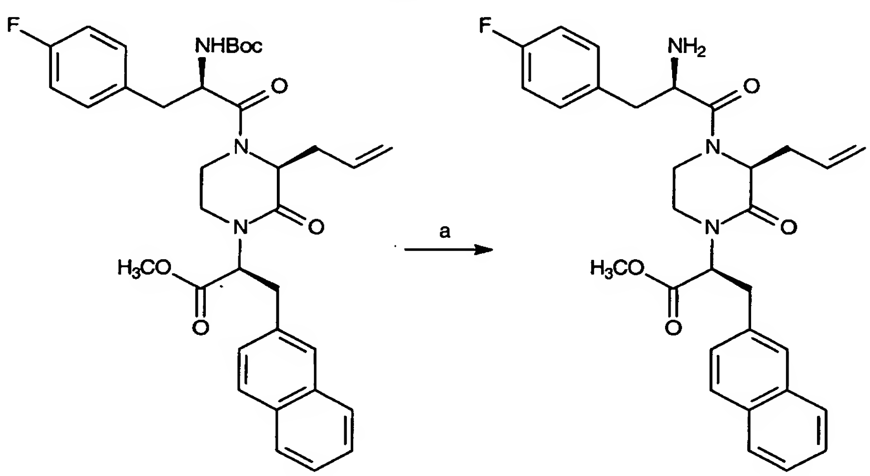
TABLE II

No.	R^1	R^4	R^8
81	methyl	-H	naphthylen-2-ylmethyl
82	ethyl	-H	naphthylen-2-ylmethyl
83	propyl	-H	naphthylen-2-ylmethyl
84	*iso*-propyl	-H	naphthylen-2-ylmethyl
85	butyl	-H	naphthylen-2-ylmethyl
86	cyclopropyl	-H	naphthylen-2-ylmethyl
87	cyclopropylmethyl	-H	naphthylen-2-ylmethyl
88	allyl	-H	naphthylen-2-ylmethyl
89	but-2-enyl	-H	naphthylen-2-ylmethyl
90	propargyl	-H	naphthylen-2-ylmethyl
91	methyl	-H	(4-chlorophenyl)methyl
92	ethyl	-H	(4-chlorophenyl)methyl
93	propyl	-H	(4-chlorophenyl)methyl
94	*iso*-propyl	-H	(4-chlorophenyl)methyl
95	butyl	-H	(4-chlorophenyl)methyl
96	cyclopropyl	-H	(4-chlorophenyl)methyl
97	cyclopropylmethyl	-H	(4-chlorophenyl)methyl
98	allyl	-H	(4-chlorophenyl)methyl
99	but-2-enyl	-H	(4-chlorophenyl)methyl
100	propargyl	-H	(4-chlorophenyl)methyl
101	methyl	$-CH_3$	naphthylen-2-ylmethyl
102	ethyl	$-CH_3$	naphthylen-2-ylmethyl
103	propyl	$-CH_3$	naphthylen-2-ylmethyl
104	*iso*-propyl	$-CH_3$	naphthylen-2-ylmethyl

105	butyl	$-CH_3$	naphthylen-2-ylmethyl
106	cyclopropyl	$-CH_3$	naphthylen-2-ylmethyl
107	cyclopropylmethyl	$-CH_3$	naphthylen-2-ylmethyl
108	allyl	$-CH_3$	naphthylen-2-ylmethyl
109	but-2-enyl	$-CH_3$	naphthylen-2-ylmethyl
110	propargyl	$-CH_3$	naphthylen-2-ylmethyl
111	methyl	$-CH_3$	(4-chlorophenyl)methyl
112	ethyl	$-CH_3$	(4-chlorophenyl)methyl
113	propyl	$-CH_3$	(4-chlorophenyl)methyl
114	*iso*-propyl	$-CH_3$	(4-chlorophenyl)methyl
115	butyl	$-CH_3$	(4-chlorophenyl)methyl
116	cyclopropyl	$-CH_3$	(4-chlorophenyl)methyl
117	cyclopropylmethyl	$-CH_3$	(4-chlorophenyl)methyl
118	allyl	$-CH_3$	(4-chlorophenyl)methyl
119	but-2-enyl	$-CH_3$	(4-chlorophenyl)methyl
120	propargyl	$-CH_3$	(4-chlorophenyl)methyl

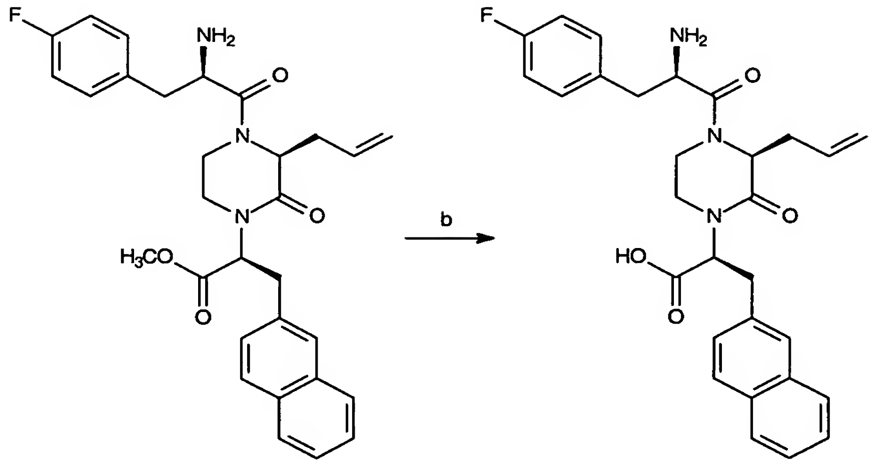
The compounds which comprise the second aspect of Category I can be prepared by the procedure outlined herein below in Scheme II which entails de-protection of intermediates such Intermediate **6** to form the ester analogs which comprise this aspect and hydrolysis of the corresponding ester analogs to the free acid analogs.

Scheme II



6 **10**

Reagents and conditions: (a) TFA, CH_2Cl_2; rt, 45 min.



10 11

Reagents and conditions: (b) LiOH, THF/MeOH/H_2O; rt, 3 hr.

EXAMPLE 2

2-{3-Allyl-4-[2-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (10)

Preparation of 2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (10): To a solution of (*S*)-2-{3-(*S*)-allyl-4-[2-(*R*)-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **6**, (200 mg, 0.324 mmol) in CH_2Cl_2 (1 mL) is added trifluoroacetic acid. The reaction mixture is stirred for 45 min, concentrated *in vacuo* and the resulting residue purified by reverse phase HPLC to afford the trifluoroacetate salt of the desired product.

EXAMPLE 3

2-{3-Allyl-4-[2-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (11)

Preparation of 2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (11): To a solution of 2-{3-allyl-4-[2-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **10**, (168 mg, 0.324 mmol) in a mixture of THF (1mL)/CH_3OH (0.5 mL)/H_2O (0.5 mL) is added LiOH (43 mg, 1.78 mmol). The reaction mixture is stirred for 3 hours, acidified with 1N HCl to pH 3 and extracted with EtOAc. The extract is dried over Na_2SO_4, filtered, concentrated and dried under high vacuum to afford the desired product in quantitative yield.

The following are non-limiting examples of other melanocortin receptor ligands encompassed by Category I of the present invention.

2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-methyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-ethyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-ethyl-4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-propyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-propyl-4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-*iso*-propyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-cyclopropylmethyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-*iso*-butyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-propargyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-benzyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-*N*,*N*-dimethyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-3-(*S*)-isopropyl-2-oxo-piperazin-1-yl}-*N*-cyclopropylmethyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-3-(*S*)-isopropyl-2-oxo-piperazin-1-yl}-*N*-cyclopropylmethyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-3-(*S*)-propyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-(4-trifluoromethylphenyl)-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-3-(*S*)-allyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-phenyl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-3-(*S*)-methyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-3-(*S*)-propyl-2-oxo-piperazin-1-yl}-*N*-(2-fluoroethyl)-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-3-(*S*)-propyl-2-oxo-piperazin-1-yl}-*N*-(2-hydroxyethyl)-3-naphthalen-2-yl-propionamide;

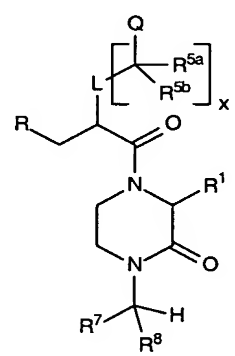
2-(*S*)-{4-[2-(*R*)-amino-3-(4-chlorophenyl)propionyl]-3-(*S*)-propyl-2-oxo-piperazin-1-yl}-*N*-(2-dimethylaminoethyl)-3-naphthalen-2-yl-propionamide;

2-(*S*)-{4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-3-(*S*)-propyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-(1*H*-indol-3-yl)-propionamide;

2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide; and

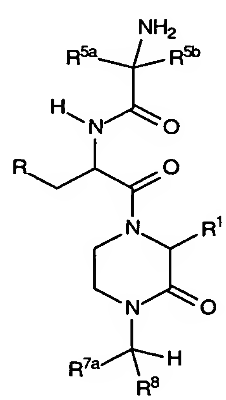
2-(*S*)-{3-(*S*)-allyl-4-[2-(*R*)-amino-3-(4-fluorophenyl)propionyl]-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide.

Category II melanocortin receptor ligands according to the present invention comprise the 2-oxo-3-hydrocarbyl-piperazines having the general scaffold with the formula:



wherein the index x can be 0 or 1.

The first aspect of Category II comprises analogs with a scaffold having the formula:



wherein R is a substituted or unsubstituted aryl unit as defined herein above and non-limiting examples of R^1, R^{5a}, R^{5b}, R^{7a} and R^8 are provided herein below in Table III.

TABLE III

No.	R^1	R^{5a}	R^{5b}	R^{7a}	R^8
121	methyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
122	ethyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
123	propyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
124	*iso*-propyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
125	butyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
126	*tert*-butyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
127	cyclopropyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
128	cyclopropylmethyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
129	allyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
130	but-2-enyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
131	methyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
132	ethyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
133	propyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
134	*iso*-propyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
135	butyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
136	*tert*-butyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
137	cyclopropyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
138	cyclopropylmethyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
139	allyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
140	but-2-enyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
141	methyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
142	ethyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
143	propyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
144	*iso*-propyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
145	butyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
146	*tert*-butyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
147	cyclopropyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
148	cyclopropylmethyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
149	allyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
150	but-2-enyl	-H	-H	$-C(O)NH_2$	(4-chlorophenyl)methyl
151	methyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl

152	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
153	propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
154	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
155	butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
156	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
157	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
158	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
159	allyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
160	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
161	methyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
162	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
163	propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
164	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
165	butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
166	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
167	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
168	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
169	allyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
170	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
171	methyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
172	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
173	propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
174	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
175	butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
176	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
177	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
178	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
179	allyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
180	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
181	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
182	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
183	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
184	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
185	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
186	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
187	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl

188	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
189	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
190	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
191	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
192	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
193	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
194	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
195	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
196	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
197	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
198	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
199	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
200	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
201	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
202	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
203	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
204	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
205	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
206	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
207	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
208	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
209	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
210	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
211	methyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
212	ethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
213	propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
214	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
215	butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
216	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
217	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
218	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
219	allyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
220	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
221	methyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
222	ethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
223	propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl

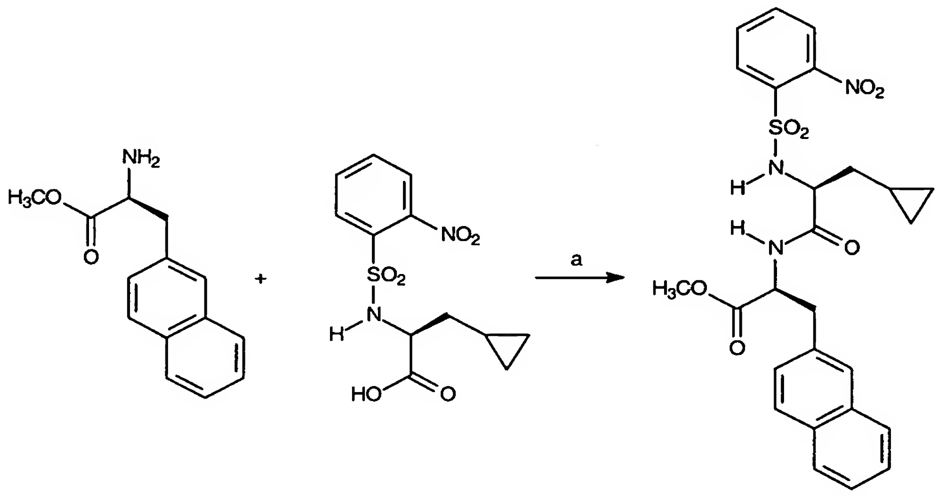
224	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
225	butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
226	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
227	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
228	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
229	allyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
230	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
231	methyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
232	ethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
233	propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
234	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
235	butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
236	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
237	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
238	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
239	allyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
240	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
241	methyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
242	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
243	propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
244	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
245	butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
246	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
247	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
248	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
249	allyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
250	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	naphthylen-2-ylmethyl
251	methyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
252	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
253	propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
254	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
255	butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
256	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
257	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
258	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
259	allyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl

260	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(3,4-dichlorophenyl)methyl
261	methyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
262	ethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
263	propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
264	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
265	butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
266	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
267	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
268	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
269	allyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
270	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NH(CH_2CH_2F)$	(4-chlorophenyl)methyl
271	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
272	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
273	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
274	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
275	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
276	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
277	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
278	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
279	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
280	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	naphthylen-2-ylmethyl
281	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
282	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
283	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
284	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
285	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
286	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
287	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
288	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
289	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
290	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(3,4-dichlorophenyl)methyl
291	methyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
292	ethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
293	propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
294	*iso*-propyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
295	butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl

296	*tert*-butyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
297	cyclopropyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
298	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
299	allyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl
300	but-2-enyl	$-CH_3$	$-CH_3$	$-C(O)NHCH(CH_3)_2$	(4-chlorophenyl)methyl

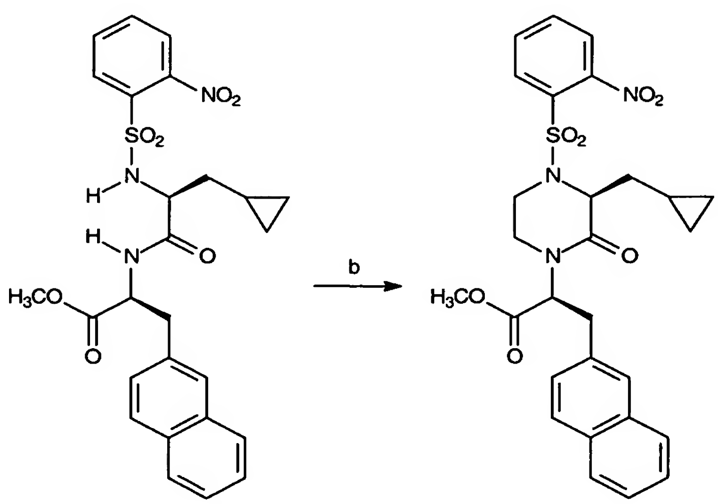
Compounds which comprise the first aspect of Category II analogs can be prepared by the procedure outlined herein below in Scheme III.

Scheme III



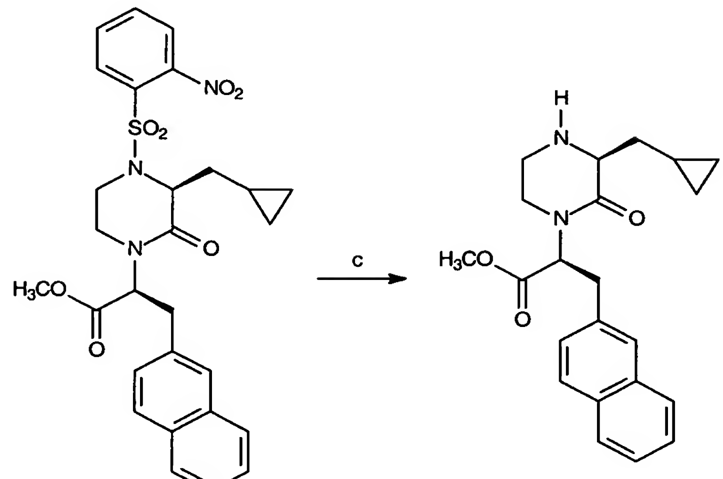
12

Reagents and conditions: (a) EDCI, HOBt, NMM; rt, 4 hr.



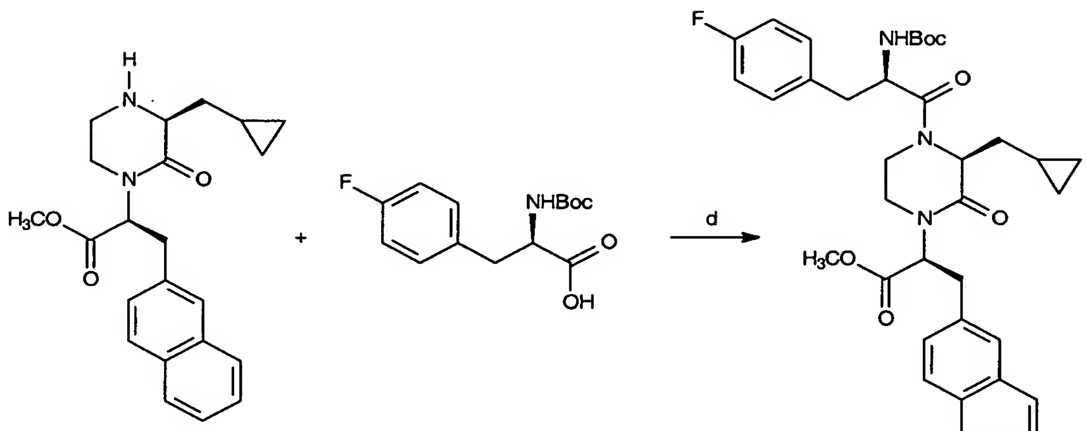
12 13

Reagents and conditions: (b) 1,2-dibromoethane, K_2CO_3, DMF; 65 °C, 15 hr.



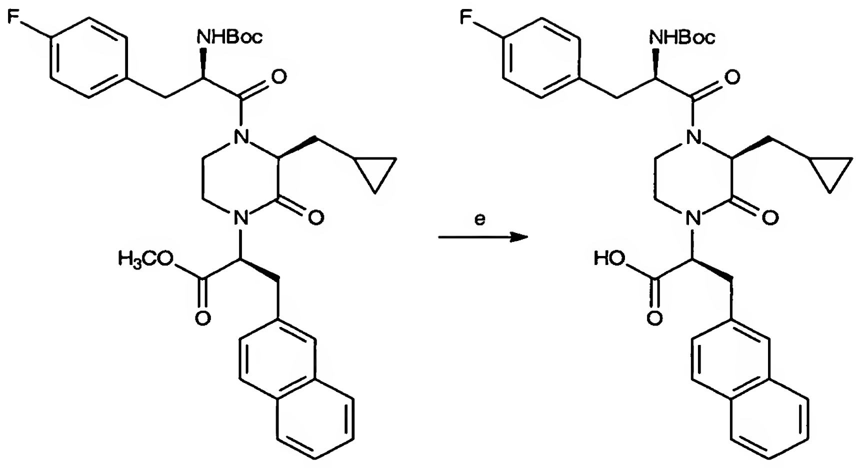
13 14

Reagents and conditions: (c) 4-mercaptophenol, K_2CO_3, DMF; rt, 15 hr.



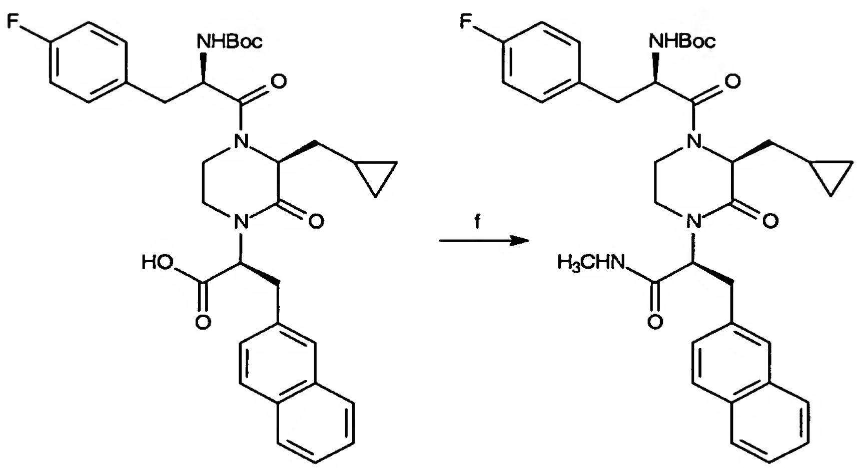
14 15

Reagents and conditions: (d) PyBOP, TEA, CH_2Cl_2; rt, 10 hr.



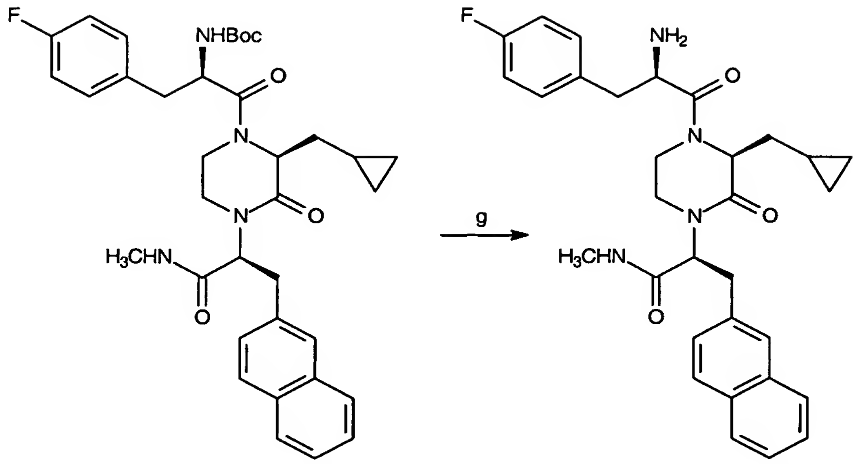
15 16

Reagents and conditions: (e) LiOH, THF/MeOH/H_2O; rt, 4 hr.



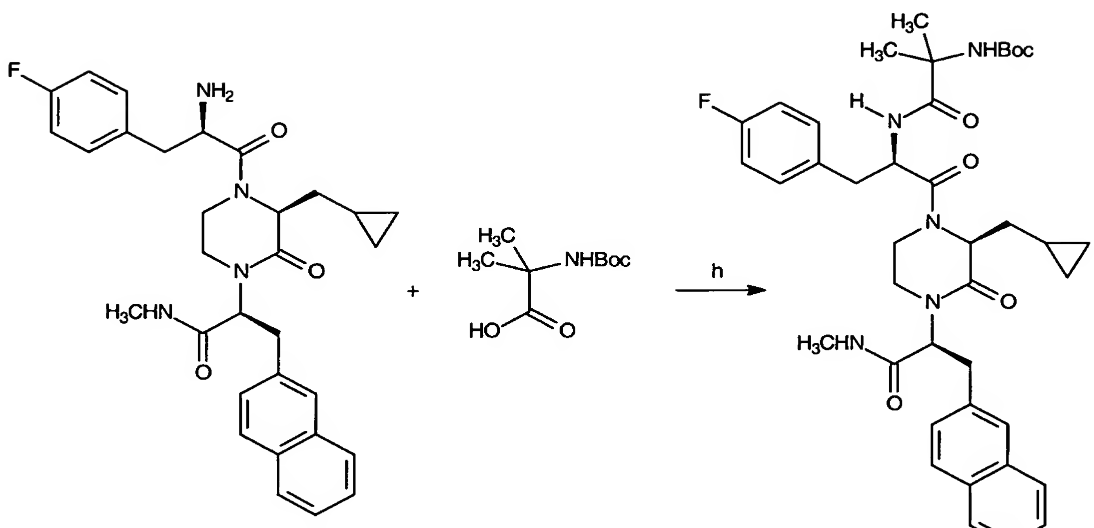
16 17

Reagents and conditions: (f) NH_2CH_3, EDCI, HOBt, NMM; rt, 3 hr.



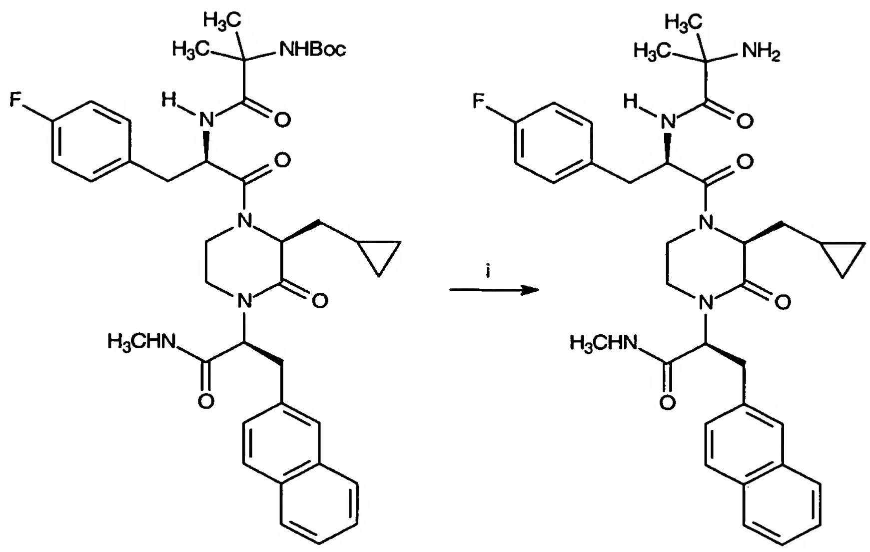
17 18

Reagents and conditions: (g) TFA/anisole/CH_2Cl_2; rt, 3 minutes.



18 19

Reagents and conditions: (h) EDCI, HOBt, NMM; rt, 3 hr.



19 20

Reagents and conditions: (i) TFA/anisole/CH_2Cl_2; rt, 1 hr.

EXAMPLE 4

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (20)

3-Cyclopropyl-2-(2-nitro-benzenesulfonylamino)-propionic acid can be prepared as follows: To a solution of 2-amino-3-cyclopropyl propionic acid (1.0g, 7.74 mmol) and triethyl amine (2.3g, 10.4 mmol) in THF/H_2O (10 ml/20 mL) is added 2-nirtobenzenesulfonyl chloride (2.3 g, 10.4 mmol) in portions at 0 °C. The reaction mixture is stirred at room temperature for 15 hours and the THF is removed *in vacuo*. The residual aqueous layer is then acidified with conc. HCl and extracted with ethyl acetate. The combined ethyl acetate extracts are dried over Na_2SO_4 and concentrated *in vacuo* to afford 2.5 g of the N-protected amino acid in purity suitable for direct use. This procedure is suitable for other amino acids which are used as a source of R^1 units. ^1H NMR (300 MHz, CD_3OD) δ 8.10-8.19 (m, 1H), 7.76-7.90 (m, 3H), 4.10-4.18 (m, 1H), 1.71-1.84 (m, 1H), 1.56-1.67 (m, 1H), 0.73-0.88 (m, 1H), 0.28-0.50 (m, 2H), 0.00-0.20 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.56, 148.10, 134.10, 133.86, 132.52, 130.42, 124.80, 57.10, 37.83, 7.23, 4.04, 3.48; MS (ESMS) *m/z* 315.0 $(M+H)^+$.

Preparation of 2-[3-cyclopropyl-2-(2-nitro-benzenesulfonylamino)-propionylamino]-3-naphthalen-2-yl-propionic acid methyl ester (12): To a solution of cyclopropyl-2-(2-nitro-benzenesulfonylamino)-propionic acid (7.74 mmol) in DMF (10 mL) are added 2-(*S*)-amino-3-naphthalen-2-yl-propionic acid methyl ester (3.1 g, 11.7 mmol), N-methylmorpholine (4.67g, 46.27 mmol), 1-hydroxybenzotriazole (17.76 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

(1.93g, 10.07mmol) consecutively. The resulting mixture is stirred for 4 hours, quenched with aqueous NH_4Cl and extracted with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified over silica gel (hexanes/ethyl acetate, 1:1) to afford 3.46 g (85 % yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 7.7, 1.4 Hz, 1H), 7.42-7.68 (m, 9H), 7.24 (dd, J = 8.4, 1.5 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.20 (d, J = 6.9 Hz, 1H), 4.84-4.96 (m, 1H), 3.98-4.07 (m, 1H), 3.71 (s, 3H), 3.29 (dd, J = 14.0, 5.6 Hz, 1H), 3.14 (dd, J = 14.0, 7.4 Hz, 1H), 1.62-1.72 (m, 1H), 1.23-1.42 (m, 1H), 0.02-0.40 (m, 3H), -0.14- -0.02(, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.74, 170.45, 147.91, 134.02, 133.73, 133.61, 133.18, 132.70, 131.07, 128.55, 128.32, 127.89, 127.41, 126.54, 126.12, 125.76, 58.59, 53.56, 52.74, 38.34, 37.55, 6.86, 4.38; MS (ESMS) *m/z* 526.1 $(M+H)^+$.

Preparation of 2-[3-cyclopropylmethyl-4-(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester (13): To a solution of 2-[3-cyclopropyl-2-(2-nitro-benzenesulfonylamino)-propionylamino]-3-naphthalen-2-yl-propionic acid methyl ester, 12, (3.46 g, 6.59 mmol) and 1,2-dibromoethane (12.38 g, 65.9 mmol) in DMF (40 mL) is added potassium carbonate (9.10 g, 65.8 mmol). The reaction mixture is stirred for 15 hours at 65 °C, cooled and quenched with aqueous NH_4Cl solution. The mixture is then extracted several times with EtOAc and the combined extracts dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue is purified over silica gel (hexanes/EtOAc, 1:2) to afford 3.57 g (98% yield) of the desired product. ^1H NMR (300 MHz, CD_3OD) δ 8.01-8.08 (m, 1H), 7.58-7.84 (m, 7H), 7.43-7.52 (m, 2H), 7.35 (dd, J = 8.4 Hz, 1H), 5.38 (dd, J = 11.7, 4.8 Hz, 1H), 4.33-4.44 (m, 1H), 3.76-3.88 (m, 1H), 3.69 (s, 3H), 3.21-3.66 (m, 4H), 2.99-3.14 (m, 1H), 1.40-1.53 (m, 1H), 1.02-1.16 (m, 1H), -0.14- -0.02 (m, 3H), -0.34 - -0.20 (m, 2H); MS (ESMS) *m/z* 552.2 $(M+H)^+$.

Preparation of 2-(3-cyclopropylmethyl-2-oxo-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester (14): To a solution of 2-[3-cyclopropylmethyl-4-(2-nitro-benzene-sulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester, **13**, (3.56 g, 6.46 mmol) and 4-mercaptophenol (4.07 g, 32.3 mmol) in CH_3CN (50 mL) is added potassium carbonate (8.91 g, 64.6 mmol). The reaction mixture is stirred for 15 hours, quenched with 10% $NaHCO_3$ solution and extracted several times with EtOAc. The combined extracts are dried over Na_2SO_4 and concentrated *in vacuo* to yielding a bright yellow oil which is purified over silica gel (hexanes/EtOAc, 1:1 to EtOAc/MeOH, 10:1) to afford 2.10 g (89% yield) of the desired product. ^1H NMR (300 MHz, CD_3OD) δ 7.76-7.86 (m, 3H), 7.71 (s, 1H), 7.37-7.52 (m, 3H), 5.27 (dd, J = 11.7, 4.8 Hz, 1H), 3.79 (s, 3H), 3.25-3.60 (m, 4H), 2.88-3.06 (m, 2H), 2.62-2.75 (m, 1H), 1.56-1.68 (m, 1H), 1.16-1.29 (m, 1H), 0.01-0.25 (m, 3H), -0.19- -0.08 (m, 2H); ^{13}C NMR (75 MHz, MeOD) δ 171.55, 171.01m 134.88, 133.78, 132.74, 128.15, 127.52, 127.45, 127.11, 126.11, 125.64, 59.42, 58.92, 51.78, 46.77, 41.23, 36.59, 33.97, 6.63, 3.72, 3.46; MS (ESMS) *m/z* 367.2 $(M+H)^+$.

Preparation of 2-{4-[2-*tert*-Butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (15): To a solution of 2-(3-cyclopropylmethyl-2-oxo-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester, **14**, (528 mg, 1.44 mmol) in CH_2Cl_2 (5.0 mL) are added 2-(*R*)-*tert*-butoxycarbonyl-amino-3-(4-fluorophenyl)propionic acid (489 mg, 1.67 mmol), benzotriazole-1-yl-oxy-tris-pyrrolidinol-phosphonium hexafluorophosphate (951 mg, 1.83 mmol) and triethyl amine (174 mg, 1.72 mmol). The reaction mixture is stirred for 10 hours, quenched with 10% $NaHCO_3$ aqueous solution and extracted several times with EtOAc. The combined extracts are dried over Na_2SO_4, filtered and concentrated in vacuo to a crude residue which is purified over silica gel (silica gel, hexanes/ethyl acetate, 1:1) to afford 651 mg (71% yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$, Rotamers) δ 7.66-7.85 (m, 3H), 7.55 (s, 1H), 7.39-7.53 (m, 2H), 7.28-7.38 (m, 1H), 7.04-7.18 (m, 2H), 6.86-7.01 (m, 2H), 5.63 (dd, J= 11.4, 5.4 Hz, 0.5H), 5.47 (dd, J = 11.4, 5.4 Hz, 0.5H), 5.28-5.38 (m, 0.5H), 4.82-4.98 (m, 1H), 4.56-4.80 (m, 1H), 4.30-4.43 (m, 0.5H), 3.75-3.91 (m, 4H), 3.50-3.62 (m, 1H), 2.92-3.36 (m, 4H), 2.64-2.88 (m, 2H), 1.38 (s, 5H), 1.35 (s, 4H), 0.91-1.18 (m, 2H), -0.64-0.17 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, Rotamers) δ 170.69, 170.54, 169.37, 168.55, 167.10,155.09, 154.84, 134.05, 133.71, 133.53, 133.49, 132.60,132.41, 131.79, 131.28, 131.17, 130.89, 130.79, 128.74, 128.66, 127.94, 127.86, 127.73, 127.63, 127.50, 127.03, 126.63, 126.57, 126.14, 115.94, 115.66, 115.56, 115.28, 80.34, 79.87, 58.82, 57.26, 56.42, 52.76, 51.66, 51.32, 44.08, 42.79, 41.36, 39.92, 38.75, 37.43, 36.72, 36.58, 34.92, 34.54, 28.44, 7.12, 4.74, 4.69, 4.34, 4.31; MS (ESMS) *m/z* 632.2 $(M+H)^+$.

Preparation of 2-{4-[2-*tert*-Butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (16): To a solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, 15, (531 mg, 0.842 mmol) in a mixture of THF (5mL)/CH_3OH (1 mL)/H_2O (2 mL) is added LiOH (100 mg, 4.17 mmol). The reaction mixture is stirred for 4 hours, acidified with 1N HCl to pH 3 and extracted several times with EtOAc. The combined extracts are dried over Na_2SO_4, filtered, concentrated *in vacuo* and dried under high vacuum to give the free acid in quantitative yield, which is used directly without further purification. ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.72-7.87 (m, 3H), 7.68 (s, 1H), 7.37-7.53 (m, 3H), 7.12-7.28 (m, 2H), 6.99-7.06 (m, 2H), 5.54-5.66 (m, 1H), 4.52-4.80 (m, 1.5H), 3.82-4.38 (m, 1.5H), 3.18-3.64 (m, 4H), 2.70-3.02 (m, 3H), 0.80-1.43 (m, 11H), -0.78-0.10 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 171.68, 171.58, 170.23, 169.29, 167.86, 163.70, 156.08, 134.69, 134.57, 133.71, 133.14, 132.70, 131.26, 131.15, 130.73, 130.64, 128.19, 128.12, 127.55, 127.38, 127.29, 127.07, 126.12, 125.64, 79.61, 79.34, 58.68, 57.04, 56.18, 52.13, 51.65,

43.21, 42.29, 41.29, 38.61, 37.32, 37.21, 36.27, 34.23, 33.93, 27.50, 27.41, 6.45, 3.92, 3.66, 3.33; MS (ESMS) *m/z* 618.2 $(M+H)^+$.

Preparation of [2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (17): To a solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid, **16**, (114 mg, 0.18 mmol)) in DMF (2 mL) are added methylamine (2M, 0.11 mL, 0.22 mmol), 1-hydroxybenzotriazole (53 mg, 0.39 mmol), N-methylmorpholine (63 mg, 0.62 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (41 mg, 0.21 mmol) consecutively. The reaction mixture is stirred for 3 hours, quenched with aqueous NH_4Cl and extracted several times with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated in vacuo to a residue, which is purified over silica gel (hexanes/ethyl acetate, 1:4) to afford 108 mg (93% yield) of the desired product. ^1H NMR (300 MHz, CD_3OD, Rotamers) δ 7.73-7.86 (m, 3H), 7.70 (s, 1H), 7.38-7.52 (m, 3H), 7.14-7.30 (m, 2H), 6.91-7.04 (m, 2H), 5.54-5.72 (m, 1H), 4.50-4.78 (m, 2H), 4.28-4.40 (m, 0.3H), 4.03-4.15 (m, 0.7H), 3.72-3.81 (m, 0.3H), 3.58-3.68 (m, 0.3H), 3.42-3.53 (m, 2H), 3.12-3.32 (m, 2H), 2.70-3.00 (m, 6H), 1.41 (s, 5H), 1.34 (s, 4H), 0.66-1.30 (m, 2H), -0.60- -0.12 (m, 4.3H), -0.80- -0.68 (m, 0.7H); MS (ESMS) *m/z* 631.3 $(M+H)^+$.

Preparation of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (18): [2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester, **17**, (105 mg, 0.16 mmol) is dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 2 mL). The reaction mixture was stirred for 3 minutes, concentrated in vacuo and the residue purified by reverse phase HPLC to afford the TFA salt of the desired compound. MS (ESMS) *m/z* 531.2 $(M+H)^+$.

Preparation of {1-[2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid *tert*-butyl ester (19): To a solution of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide, **18**, (44 mg, 0.068 mmol) in DMF (1 mL) are added 2-*tert*-butoxycarbonylamino-2-methyl-propionic acid (44 mg, 0.079 mmol), 1-hydroxybenzotriazole (20 mg, 0.148 mmol), N-methylmorpholine (41 mg, 0.41 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (16 mg, 0.083 mmol) consecutively. The reaction mixture is stirred for 3 hours, quenched with aqueous NH_4Cl and extracted several times with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated

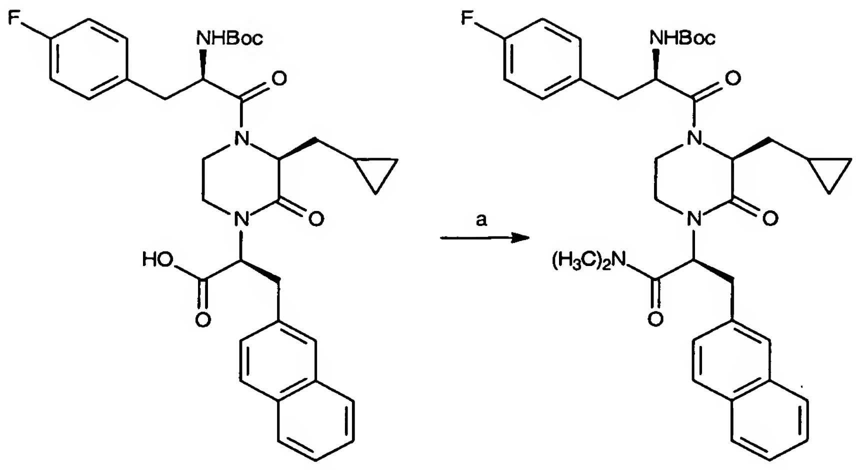
in vacuo to a residue which is purified over silica gel (CH_2Cl_2/CH_3OH, 13:1) to afford 45 mg (93% yield) of the desired product. MS (ESMS) *m/z* 716.3 $(M+H)^+$.

Preparation of 2-{4-[2-(2-amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (20). {1-[2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid *tert*-butyl ester, **19**, (45 mg, 0.063 mmol) is dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 1 mL). The reaction mixture is stirred for 1 hour, concentrated *in vacuo* and the residue purified by reverse phase HPLC purification to afford the TFA salt of the desired compound. ^1H NMR (300 MHz, CD_3OD, Rotamers) δ 7.65-7.84 (m, 4H), 7.36-7.52 (m, 3H), 7.15-7.31 (m, 2H), 6.90-7.02 (m, 2H), 5.73 (dd, J = 11.7, 5.4 Hz, 0.66H), 5.60 (dd, J = 11.4, 5.4 Hz, 0.33H), 5.01-5.14 (m, 0.66H), 4.65-4.75 (m, 0.33H), 4.24-4.36 (m, 0.33H), 4.01-4.14 (m, 0.66H), 3.82-3.98 (m, 0.66H), 3.14-3.68 (m, 5H), 2.73-3.10 (m, 6H), 1.25-1.60 (m, 7H), 0.78-0.95 (m, 1H), -0.56- -0.15 (m, 4H), -0.76- -0.62 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 171.66, 171.04, 170.86, 170.34, 169.54, 169.29, 167.78, 163.81, 160.57, 134.36, 133.70, 132.74, 132.21, 131.22, 131.11, 130.89, 130.78, 128.16, 127.69, 127.51, 127.31, 127.10, 126.17, 125.70, 115.47, 115.14, 114.85, 58.73, 56.98, 56.84, 56.42, 56.32, 51.61, 50.96, 48.75, 42.12, 41.62, 37.86, 37.47, 37.25, 36.46, 36.36, 34.57, 34.35, 25.32, 23.05, 22.91, 22.73, 6.56, 3.96, 3.73, 3.40; MS (ESMS) *m/z* 616.2 $(M+H)^+$.

The above example wherein 3-cyclopropyl-2-(*S*)-(2-nitro-benzenesulonylamino)-propionic acid is used for the preparation of compound **12**, provides one iteration of the analogs encompassed by the first aspect of Category II. Other examples encompassed within the first aspect of Category II, wherein R^1 comprises other units, can be suitably prepared by substituting the appropriate starting material in place of 3-cyclopropyl-2-(*S*)-(2-nitro-benzenesulonylamino)-propionic acid, for example, cyclopropyl-2-(*S*)-(nitro-benzene-sulonylamino)-acetic acid, 2-(*S*)-(2-nitro-benzenesulonylamino)-butyric acid, and the like. The formulator may also choose to prepare rings which comprise the opposite stereochemistry, for example, those derived from the use of 3-cyclopropyl-2-(*R*)-(2-nitro-benzenesulonylamino)-propionic acid or, as a further iteration, the formulator may wish to provide a racemic mixture, for example, an analog derived from, 3-cyclopropyl-2-(*R,S*)-(2-nitro-benzenesulonylamino)-propionic acid.

Other iterations of this aspect of the present invention, for example, wherein R^{7a} is varied, can be prepared by the procedure outlined herein below in Scheme IV beginning with compounds such as intermediate **16**.

Scheme IV



16 21

Reagents and conditions: (a) $NH(CH_3)_2$, EDCI, HOBt, NMM; rt, 4 hr.

The following are non-limiting examples of compounds which comprise the first aspect of Category II according to the present invention.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-(2-fluoroethyl)-3-naphthalen-2-yl-propion-amide: ^1H NMR (300 MHz, CD_3OD, Rotamers) δ 8.40-8.61 (m, 0.6H), 7.53-7.92 (m, 4H), 7.38-7.57 (m, 3H), 7.15-7.36 (m, 2H), 6.90-7.10 (m, 2H), 5.60-5.87 (m, 1H), 5.46-5.58 (m, 0.4H), 5.01-5.15 (m, 0.6H), 4.21-4.78 (m, 3H), 3.88-4.15 (m, 1H), 3.16-3.76 (m, 7H), 2.80-3.13 (m, 2H), 1.35-1.59 (m, 6H), 0.76-1.27 (m, 2H), -0.76- -0.09 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 173.62, 172.82, 172.60, 172.41, 171.92, 171.13, 170.90, 169.45, 165.45, 165.38, 162.81, 162.21, 162.15, 135.84, 135.26, 134.33, 134.22, 134.18, 133.86, 133.84, 132.76, 132.65, 132.39, 132.29, 129.74, 129.26, 129.12, 129.06, 128.86, 128.69, 128.61, 127.73, 127.26, 117.04, 116.68, 116.40, 84.51, 82.29, 60.39, 58.50, 58.05, 57.85, 53.24, 52.55, 43.70, 43.32, 41.66, 41.38, 39.50, 38.92, 38.84, 38.08, 37.90, 36.24, 36.11, 24.45, 24.27, 24.19, 8.20, 8.10, 5.49, 5.29, 4.90; MS (ESMS) *m/z* 648.9 $(M+H)^+$.

3-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-methyl-4-naphthalen-2-yl-butyramide. ^1H NMR ($CDCl_3$, 300 MHz) 6.80~7.80 (m, 11H), 5.06 (m, 2H), 4.58 (m, 1H), 2.50~3.50 (m, 13H), 1.54 (m, 6H), 0.91(m, 2H). ^{13}C NMR ($CDCl_3$, 75 mHz) 171.90, 171.79, 169.93, 168.70, 134.59, 133.58, 132.62, 131.43, 131.22, 128.45, 127.90, 127.56, 127.26, 126.61, 126.08, 115.80, 115.51, 57.61, 56.03, 50.70, 40.98, 38.69, 38.01, 37.62, 34.05, 26.54, 24.42, 24.18, 23.21, 18.73, 13.50; MS (ES-MS) *m/z* 618 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (CD_3OD, 300 MHz) 7.81-7.70, m, 4H; 7.48-7.39, m, 3H; 7.25, m, 2H; 6.98, m, 2H; 5.67-5.56, m, 1H; 5.06, m, 0.75H, 4.57, m, 0.75H; 4.23-3.96, m, 1H; 3.82-3.63, m, 1.25H; 3.44-3.16, m, 4H; 3.00-2.76, m, 6.5H; 1.54, s, 3H; 1.47, s, 3H; 1.35-0.92, m, 2.25H; 0.41-0.27, m, 5H. ^{13}C NMR (CD_3OD, 300 mHz) 171.68, 171.05, 170.13, 169.33, 160.58, 134.28, 133.75, 132.82, 132.43, 131.20, 131.10, 128.12, 127.57, 127.33, 127.05, 126.20, 125.69, 115.16, 114.88, 58.43, 56.93, 56.11, 56.01, 50.90, 41.72, 41.43, 36.57, 34.49, 34.14, 25.28, 23.04, 22.89, 22.70, 18.59, 18.36, 12.63. MS(ESI) m/e 604 [M+1].

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-(2-fluoroethyl)-propionamide trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.28 (m, 6H), 7.03 (m, 2H), 5.53 (m, 1H), 5.08 (t, 1H, J = 7.8 Hz), 4.66 (t, 1H, J = 6.6 Hz), 4.53 (m, 1H), 4.37 (m, 1H), 3.98 (m, 1H), 3.65-3.00 (m, 9H), 1.55 (s, 3H), 1.45 (s, 3H), 1.29 (m, 2H), 0.80 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.5, 172.5, 172.0, 171.1, 165.4, 163.0, 162.5, 162.2, 137.1, 134.3, 134.1, 133.9, 132.8, 132.7, 132.2, 130.1, 117.0, 116.7, 116.5, 84.5, 82.3, 60.2, 58.5, 58.1, 57.8, 57.7, 53.1, 52.6, 43.4, 43.1, 41.6, 41.3, 39.7, 38.8, 38.1, 36.9, 36.0, 35.5, 35.4, 24.6, 24.3, 20.5, 20.2, 14.6; MS *m/z* (ESI): 620 (M + H, 100), 622 (M + 2 + H, 37).

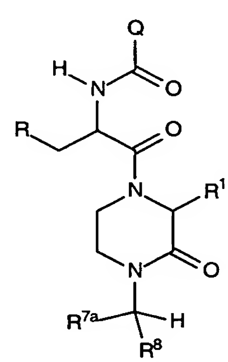
2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(R)-(4-fluorophenyl)-propionyl]-3-(S)-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.63-7.53 (m, 3H) 7.43 (s, 1H) 7.33-7.23 (m, 3H), 7.20-7.13 (m, 2H), 7.00-6.87 (m, 2H) 6.84-6.76 (m, 1H) 6.68 (t, 1H, J=8.29 Hz) 5.78 (d, 1H, J=7.25 Hz) 5.68 (d, 1H, J=7.70 Hz) 5.24-5.04 (m, 2H) 4.92-4.76 (m, 2H) 4.69 (t, 1H, J=5.90 Hz) 4.22-4.10 (m, 1H) 3.95-3.78 (m, 2H) 3.64 (t, 2H, J=6.75 Hz) 3.54-3.46 (m, 2H) 2.70 (d, 2H, J=6.98 Hz) 1.52 (s, 6H) 1.04-0.92 (m, 3H) 0.91 (d, 4H, J=2.654 Hz) MS (ESI) m/z 625 ($M+H^+$, 100).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-(4-isopropoxy-phenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.76 (m, 3H), 1.29 (m, 6H, $CH(CH_3)_2$), 1.46, 1.562 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.73, 2.80 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.06 (m, 5H), 3.33 (m, 4H), 3.63 (m, 1H), 5.10 (m, 2H), 5.48 (m, 1H), 6.83 (m, 2H), 7.02 (m, 2H), 7.14 (m, 2H), 7.30 (m, 1H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 45.26; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.8, 132.7, 132.4, 131.4, 119.0, 117.3, 116.7, 116.5, 111.8, 71.3, 61.3, 60.0, 57.9, 57.6, 43.3, 43.0, 38.5, 38.0, 35.8, 35.1, 31.5, 39.9, 26.7, 25.3, 22.8, 20.2, 14.6; MS *m/e* 612 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-(4-benzyloxy-phenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.78 (m, 3H), 1.24 (m, 2H), 1.462, 1.56 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.73, 2.81 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.00 (m, 5H), 3.17 (m, 3H), 3.62 (m, 1H), 3.963 (m, 1H), 4.65 (m, 1H), 5.06 (m, 3H), 5.47 (m, 1H), 6.93 (m, 2H), 7.03 (m, 2H), 7.162 (m, 2H), 7.03 (m, 3H), 7.40 (m, 4H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 45.31; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.8, 131.4, 129.9, 129.3, 128.9, 116.7, 116.5, 116.3, 71.4, 61.3, 58.0, 57.6, 52.1, 43.4, 43.0, 38.5, 35.8, 35.2, 31.5, 26.7, 25.3, 20.2, 14.6; MS *m/e* 660 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-4-(4-chlorophenyl)-N-methyl-butyramide · TFA. ^{1}H NMR (CD_3OD, with rotamers) δ 7.14 (m, 6H), 6.88 (m, 2H), 5.00 (m, 1H), 4.00 (m, 1H), 3.46 (m, 1H), 3.25 (m, 2H), 2.93 (m, 4H), 2.58, 2.53 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.42 (m, 2H), 1.94 (m, 2H), 1.56 (m, 2H), 1.42, 1.39, 1.32, 1.28 (4 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.05 (m, 2H), 0.76 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.2, 173.0, 172.0, 171.4, 165.4, 162.2, 141.1, 134.2, 133.5, 132.8, 132.7, 131.5, 130.0, 116.8, 116.5, 113.3, 58.5, 57.5, 57.3, 53.2, 52.5, 43.9, 42.3, 38.2, 36.8, 35.8, 33.0, 31.3, 26.7, 24.6, 24.3, 20.7, 14.5; MS *m/z* (ESI): 602 (M + H, 100), 604 (M + 2 + H, 37).

A second aspect of Category II melanocortin receptor ligands according to the present invention comprise the 2-oxo-3-hydrocarbyl-piperazines having the general scaffold with the formula:



wherein R is a substituted or unsubstituted aryl as defined herein above and non-limiting examples of R^1, R^{7a}, R^8 and Q are provided herein below in Table IV. THQ-3-yl represents 1,2,3,4-tetrahydroisoquinolin-3-yl.

TABLE IV

No.	R^1	Q	R^{7a}	R^8

300	methyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
301	ethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
302	propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
303	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
304	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
305	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
306	allyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	naphthylen-2-ylmethyl
307	methyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
308	ethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
309	propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
310	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
311	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
312	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
313	allyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
314	methyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
315	ethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
316	propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
317	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
318	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
319	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
320	allyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
321	methyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
322	ethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
323	propyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
324	*iso*-propyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
325	cyclopropyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
326	cyclopropylmethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
327	allyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
328	methyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
329	ethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
330	propyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
331	*iso*-propyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
332	cyclopropyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
333	cyclopropylmethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
334	allyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
335	methyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl

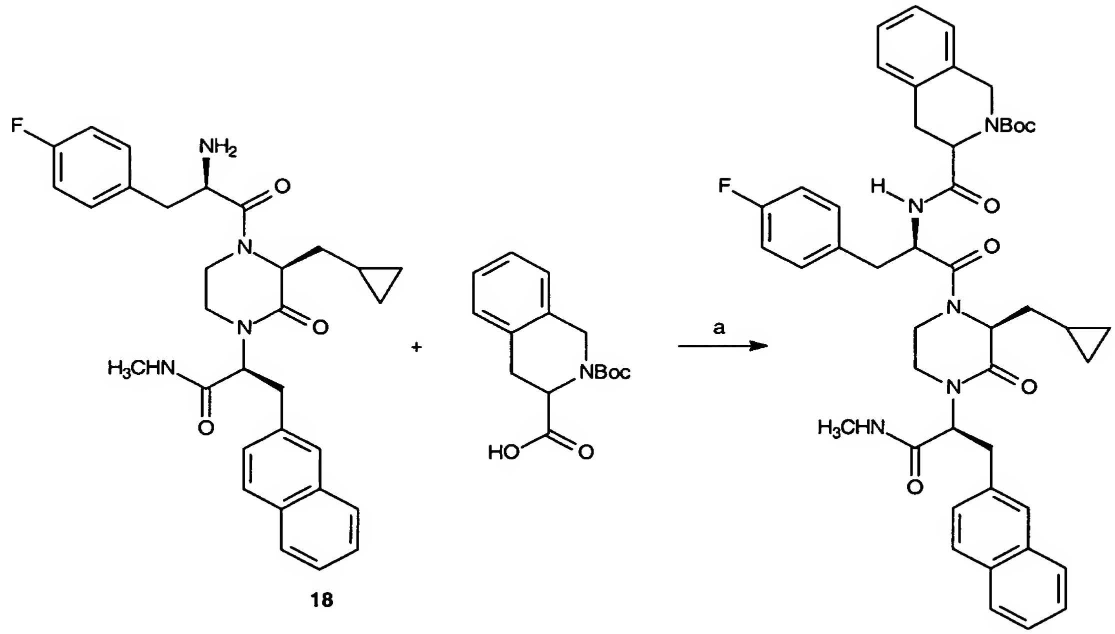
336	ethyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
337	propyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
338	*iso*-propyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
339	cyclopropyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
340	cyclopropylmethyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
341	allyl	THQ-3-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
342	methyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
343	ethyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
344	propyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
345	*iso*-propyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
346	cyclopropyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
347	cyclopropylmethyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
348	allyl	pyrrolidin-2-yl	-C(O)NH$_2$	naphthylen-2-ylmethyl
349	methyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
350	ethyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
351	propyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
352	*iso*-propyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
353	cyclopropyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
354	cyclopropylmethyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
355	allyl	pyrrolidin-2-yl	-C(O)NH$_2$	(3,4-dichlorophenyl)methyl
356	methyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
357	ethyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
358	propyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
359	*iso*-propyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
360	cyclopropyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
361	cyclopropylmethyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
362	allyl	pyrrolidin-2-yl	-C(O)NH$_2$	(4-chlorophenyl)methyl
363	methyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
364	ethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
365	propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
366	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
367	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
368	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
369	allyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
370	methyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
371	ethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl

372	propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
373	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
374	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
375	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
376	allyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
377	methyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
378	ethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
379	propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
380	*iso*-propyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
381	cyclopropyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
382	cyclopropylmethyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
383	allyl	2-aminopyrrolidin-5-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
384	methyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
385	ethyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
386	propyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
387	*iso*-propyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
388	cyclopropyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
389	cyclopropylmethyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
390	allyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
391	methyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
392	ethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
393	propyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
394	*iso*-propyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
395	cyclopropyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
396	cyclopropylmethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
397	allyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
398	methyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
399	ethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
400	propyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
401	*iso*-propyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
402	cyclopropyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
403	cyclopropylmethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
404	allyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
405	methyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
406	ethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
407	propyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl

410	*iso*-propyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
411	cyclopropyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
412	cyclopropylmethyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
413	allyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
414	methyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
415	ethyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
416	propyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
417	*iso*-propyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
418	cyclopropyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
419	cyclopropylmethyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
420	allyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
421	methyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
422	ethyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
423	propyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
424	*iso*-propyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
425	cyclopropyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
426	cyclopropylmethyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
427	allyl	pyrrolidin-2-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl

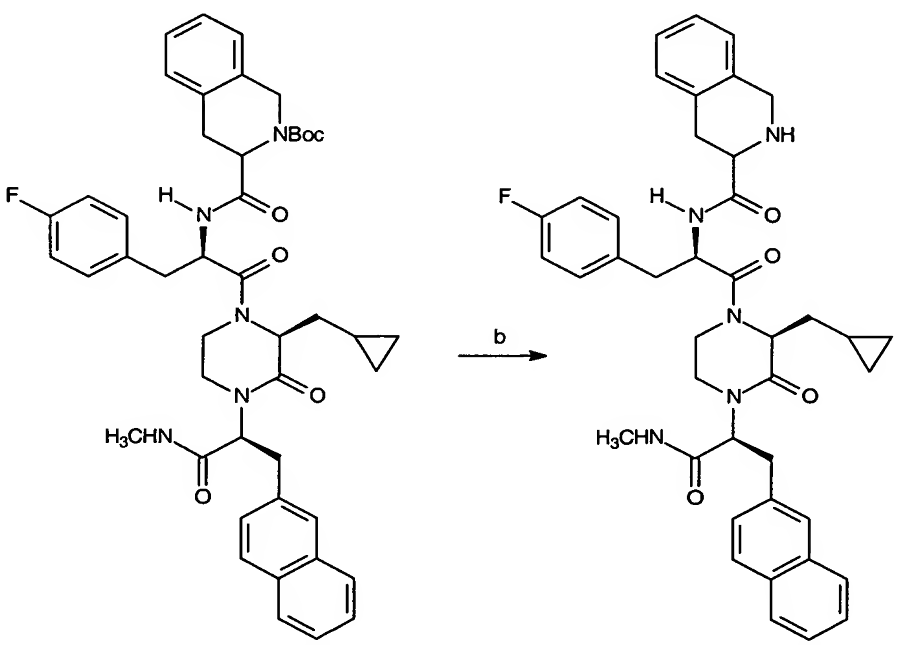
The compounds which comprise the second aspect of Category II can be suitably prepared according to Scheme V below from final analogs which comprise Category I, for example, utilizing as starting materials compounds such as **18**.

Scheme V



18 22

Reagents and conditions: (a) EDCI, HOBt, NMM; rt, 3 hr.



22 23

Reagents and conditions: (b) TFA/anisole/CH_2Cl_2; rt, 1 hr.

EXAMPLE 5

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide (23)

Preparation of 3-[2-[2-cyclopropylmehtyl-4-(1-methylcarbamoyl-2-naphthylen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenxyl)-2-oxo-ethylcarbamoyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (22): To a solution of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide, **18**, (44 mg, 0.068 mmol) in DMF (1 mL) are added 3,4-dihydro-1*H*-isoquinoline-2,3-dicarboxylic acid 2-*tert*-butyl ester (21 mg, 0.079 mmol), 1-hydroxybenzo-triazole (20 mg, 0.148 mmol), N-methylmorpholine (41 mg, 0.41 mmol) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (16 mg, 0.083 mmol) consecutively. The reaction mixture is stirred for 3 hours, quenched with aqueous NH_4Cl and extracted several times with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated in vacuo to a residue, which is purified over silica gel (CH_2Cl_2/CH_3OH, 13:1) to afford the desired product.

Preparation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid [2-[2-cyclopropyl-methyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide (23): 3-[2-[2-cyclopropylmehtyl-4-(1-methylcarbamoyl-2-naphthylen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester, **22**, (50 mg, 0.064 mmol) is dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 1 mL). The reaction mixture is stirred for 1 hour, concentrated *in vacuo* and the residue purified by reverse phase HPLC purification to afford the TFA salt of the desired compound.

Pyrrolidine-2-carboxylic acid (1R-(4-fluorobenzyl)-2-{4-[1-methylcarbamoyl-2S-(4-trifluoromethyl-phenyl)-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-2-oxo-ethyl)-amide: ^1H NMR (CD_3OD, 300 MHz) δ 7.60 (d, 2H, J=7.95 Hz) 7.46 (d, 2H, J=7.87 Hz) 7.34-7.18 (m, 2H) 7.08-6.94(m, 2H) 5.58 (q, 1H, J=5.61 Hz) 5.13 (t, 1H, J=7.76 Hz) 4.69 (t, 1H, J=6.58 Hz) 4.23 (t, 1H, J=6.69 Hz) 4.10-3.88 (m, 2H) 3.71-3.44 (m, 2H) 3.23-2.83 (m, 4H) 2.74 (s, 3H) 2.41-2.25 (m, 2H) 2.09-1.68 (m, 6H) 1.29-1.08 (m, 2H) 0.84-0.63 (m, 3H) MS (ESI) m/z 634 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid [2-{4-[1-allylcarbamoyl-2S-(4-chlorophenyl)-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-1R-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (CD_3OD, 300 MHz) δ 7.40-6.92 (m, 8H), 5.92-5.73 (m, 1H), 5.56-5.38 (m, 2H), 5.25-4.50 (m, 3H), 4.28-2.84 (m, 1H), 2.45-2.25 (m, 2H), 2.12-1.69 (m, 4H), 1.51-0.72 (m, 7H), MS (ESI) m/z 626 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid [2-{4-[2S-(4-chlorophenyl)-1-phenylcarbamoyl-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-1R-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.13-6.82 (m, 13 H) 5.12-4.62 (m, 2H) 4.50-2.68 (m, 12H) 2.30-1.48 (m, 4H) 1.35-0.58 (m, 8H) MS (ESI) m/z 684 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid [2-{4-[2S-(4-chlorophenyl)-1-ethylcarbamoyl-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-1S-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.42-6.93 (m, 8H) 5.62-5.31 (m, 1H) 5.13 (t, 1H, J=7.77 Hz) 4.80-3.88 (m, 2H) 3.71-2.76 (m, 10H) 2.51-1.55 (m, 8H) 1.40-0.65 (m, 8H) MS (ESI) m/z 614 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid [2-[4-(1-allylcarbamoyl-2S-naphthalen-2-yl-ethyl)-3-oxo-2S-propyl-piperazin-1-yl]-1R-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, 300 MHz) δ 5.99-5.50 (m, 3H) 5.28-4.50 (m, 3H) 4.28-2.72 (m, 13 H) 2.41-1.62 (m, 4H) 1.20 (t, 2H, J=7.102 Hz) 1.06-0.82 (m, 2H) 0.70-0.21 (m, 3H) (ESI) m/z 642 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid {1R-(4-fluorobenzyl)-2-[4S-(2-naphthalen-2-yl-1-phenylcarbamoyl-ethyl)-3-oxo-2S-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.92-6.88 (M, 16H) 5.90-5.65 (m, 2H) 5.28-4.51(m, 5H) 4.28-2.78(m, 7H) 2.42-2.20 (m, 2H) 2.08-1.70 (m, 4H) 1.48-0.23 (m, 5H) (ESI) m/z 678 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(4-isopropoxy-phenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-2-oxo-ethyl)-amide: ^{1}H NMR (300MHz, CD_3OD) δ 0.789 (m, 3H), 1.768 (m, 6H, $CH(CH_3)_2$), 1.789 (m, 1H), 1.974 (m, 2H), 2.333 (m, 2H), □ 2.743, 2.805 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.001 (m, 3H),. 3.173 (m, 3H), 3.340 (m, 2H), 3.659 (m, 1H), 4.024 (m, 1H), 4.232 (m, 1H), 4.560 (m, 1H), 4.679 (m, 1H), 5.135 (t, 1H), 5.473 (m, 1H), 6.826 (m, 2H), 7.039 (m, 2H), 7.136 (m, 2H), 7.316 (m, 1H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 45.392; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.4, 163.6, 163.1, 162.2, 158.7, 133.9, 133.6, 132.8, 132.7, 132.5, 132.4, 131.5, 131.4, 129.8, 120.5, 117.3, 117.1, 116.7, 116.4, 71.3, 61.3, 57.9, 57.6, 52.1, 43.3, 43.0, 38.5, 36.9, 35.8, 35.3, 35.2, 31.5, 26.7, 25.3, 22.8, 20.4, 20.2, 14.6; MS *m/e* 724 (M+1).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(4-benzyloxy-phenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (300MHz, CD_3OD) δ 0.791 (m, 3H), 1.276 (m, 2H), 1.802 (m, 1H), 1.963 (m, 2H), 2.369 (m, 1H), 2.741, 2.803 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.029 (m, 3H), 3.147 (m, 3H), 3.454 (m, 1H), 3.653 (m, 1H), 4.228 (m, 1H), 5.060 (m, 3H), 5.463 (m, 1H), 6.949 (m, 2H), 7.045 (m, 2H), 7.179 (m, 3H), 7.329 (m, 3H), 7.429 (m, 3H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 45.451; ^{13}C

NMR (75MHz, CD_3OD with rotamers) δ 165.5, 162.2, 159.7, 139.1, 133.9, 133.6, 132.8, 132.7, 132.5, 132.4, 131.6, 131.5, 130.4, 129.9, 129.3, 128.9, 117.0, 116.8, 116.5, 116.4, 71.4, 61.4, 60.1, 58.5, 58.1, 57.6, 52.7, 52.1, 43.4, 43.0, 38.5, 35.8, 35.1, 31.5, 26.7, 25.3, 20.4, 20.2, 14.6; MS *m/e* 673 (M+1).

Pyrrolidine-2-carboxylic acid [2-[4-(1-ethylcarbamoyl-2S-naphthalen-2-yl-ethyl)-3-oxo-2S-propyl-piperazin-1-yl]-1R-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (CD_3OD, 300 MHz) δ 7.79-6.89 (m, 11H) 5.69-5.45 (m, 1H) 5.09 (t, 1H, J=7.87 Hz) 4.57 (t, 1H, J=6.67 Hz) 4.28-2.70 (m, 13H) 2.08-1.62 (m, 4H) 1.20-0.16 (m, 10H) (ESI) m/z 630 ($M+H^+$, 100).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(4-chlorophenyl)-1-(2-fluoroethylcarbamoyl)-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^1H NMR (CD_3OD, with rotamers) δ 7.17 (m, 6H), 6.92 (m, 2H), 5.38 (m, 1H), 5.01 (t, 1H, *J* = 7.9 Hz), 4.57 (t, 1H, *J* = 6.7 Hz), 4.44 (m, 1H), 4.26 (m, 1H), 4.10 (m, 1H), 3.88 (m, 1H), 3.43-2.75 (m, 11H), 2.22 (m, 1H), 1.89-1.61 (m, 3H), 1.15 (m, 2H), 0.69 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.3, 172.1, 171.9, 171.7, 171.0, 169.7, 169.5, 165.5, 162.9, 162.2, 137.2, 134.2, 133.9, 133.6, 132.8, 132.7, 132.5, 132.3, 132.2, 130.0, 117.1, 116.8, 116.5, 84.6, 82.4, 61.3, 60.2, 58.1, 57.9, 57.7, 52.7, 52.1, 47.8, 43.5, 43.0, 41.6, 41.3, 39.7, 39.3, 38.5, 37.0, 35.9, 35.3, 31.6, 25.3, 20.4, 20.2, 14.6; MS *m/z* (ESI): 632 (M + H, 100), 634 (M + 2 + H, 37).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (300 MHz, MeOD, Rotamers) δ 7.40-4.49 (m, 2H), 7.17-7.35 (m, 3H), 6.92-7.10 (m, 2H), 5.39-5.55 (m, 1H), 5.08-5.20 (m, 1H), 4.65-4.74 (m, 1H), 4.15-4.30 (m, 1H), 3.99-4.12 (m, 1H), 3.42-3.69 (m, 1H), 2.89-3.40 (m, 7H), 2.81 (s, 0.6H), 2.74 (s, 2.4H), 2.26-2.42 (m, 1H), 1.69-2.10 (m, 3H), 1.15-1.62 (m, 2H), 0.69-1.13 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.00, 171.88, 171.82, 171.68, 170.92, 169.80, 169.52, 169.40, 165.47, 162.78, 162.30, 162.23, 139.44, 133.85, 133.81, 133.66, 132.82, 132.71, 132.62, 132.49, 132.38, 132.24, 132.00, 117.03, 116.79, 116.51, 61.32, 60.05, 57.59, 57.55, 52.11, 52.68, 52.11, 47.76, 43.34, 42.98, 42.90, 39.53, 39.34, 38.54, 37.08, 35.96, 35.11, 34.85, 31.59, 26.82, 25.29, 20.45, 20.25, 14.66; (ESMS) *m/z* 634.2, 636.2, 638.2 $(M+H)^+$, Cl_2 isotope pattern.

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (300 MHz, MeOD, Rotamers) □ 7.40-4.49 (m, 2H), 7.17-7.35 (m, 3H), 6.92-7.10 (m, 2H), 5.39-5.55 (m, 1H), 5.08-5.20 (m, 1H), 4.65-4.74 (m, 1H), 4.15-4.30 (m, 1H), 3.99-4.12 (m, 1H), 3.42-3.69 (m, 1H), 2.89-3.40 (m, 7H), 2.81 (s, 0.6H), 2.74 (s, 2.4H), 2.26-2.42 (m, 1H), 1.69-2.10 (m, 3H), 1.15-

1.62 (m, 2H), 0.69-1.13 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 171.00, 171.88, 171.82, 171.68, 170.92, 169.80, 169.52, 169.40, 165.47, 162.78, 162.30, 162.23, 139.44, 133.85, 133.81, 133.66, 132.82, 132.71, 132.62, 132.49, 132.38, 132.24, 132.00, 117.03, 116.79, 116.51, 61.32, 60.05, 57.59, 57.55, 52.11, 52.68, 52.11, 47.76, 43.34, 42.98, 42.90, 39.53, 39.34, 38.54, 37.08, 35.96, 35.11, 34.85, 31.59, 26.82, 25.29, 20.45, 20.25, 14.66; (ESMS) *m/z* 634.2, 636.2, 638.2 $(M+H)^+$, Cl_2 isotope pattern.

The following are non-limiting examples of compounds encompassed by the second aspect of Category II.

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-4-chlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-methyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide;

Pyrrolidine-2-carboxylic acid [2-[2-allyl-4-(1-methylcarbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide; and

Pyrrolidine-2-carboxylic acid [2-[2-*iso*-propyl-4-(1-methyl-carbamoyl-3,4-dichlorophenyl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide.

The following are examples of compounds wherein R^{7a} is hydrogen:

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-[4-(2-naphthalen-2-yl-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.74-7.88 (m, 3H), 7.68 (s, 1H), 7.18-7.54 (m, 11H), 5.04-5.28 (m, 1H), 4.78-4.88 (m, 1H), 4.31-4.47 (m, 2H), 3.88-4.25 (m, 3H), 3.31-3.66 (m, 2H), 2.70-3.30 (m, 8H), 0.92-1.86 (m, 4H), 0.76-0.88 (m, 3H); ^{13}C NMR (75 MHz, MeOD, Rotamers) δ 171.62, 171.43, 170.49, 169.64, 169.30, 168.78, 137.81, 137.65, 136.72, 136.15, 135.42, 135.35, 134.70, 134.51, 134.22, 132.70, 132.42, 132.05, 131.91, 130.35, 130.10, 129.77, 129.64, 129.54, 129.16, 129.10, 129.04, 128.86, 128.78, 128.09, 127.62, 127.56, 127.01, 59.98, 56.94, 56.66, 56.54, 51.82, 51.65, 49.74, 49.41, 48.28, 47.22, 45.78, 41.56, 39.92, 38.68, 37.21, 36.17, 35.42, 34.66, 34.43, 31.38, 31.29, 20.74, 20.50, 14.56; MS (ESMS) *m/z* 637.3, 639.3 $(M+H)^+$, Cl isotope pattern.

2-Amino-N-{1-(4-chlorobenzyl)-2-[4-(2-naphthalen-2-yl-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-2-methyl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.74-7.88 (m, 3H), 7.67 (s, 1H), 7.36-7.54 (m, 3H), 7.14-7.35 (m, 4H), 5.07-5.18 (m, 0.7H), 4.93-

5.03 (m, 0.3H), 4.73-4.84 (m, 1H), 4.30-4.41 (m, 0.3H), 3.86-4.09 (m, 2H), 3.38-3.64 (m, 2H), 2.68-3.26 (m, 6H), 0.91-1.82 (m, 10H), 0.74-0.88 (m, 3H); ^{13}C NMR (75 MHz, MeOD, Rotamers) δ 173.35, 172.93, 171.80, 171.61, 170.49, 168.78, 137.78, 137.65, 136.84, 136.36, 135.41, 135.35, 134.61, 134.43, 134.22, 132.58, 132.29, 130.30, 130.03, 129.64, 129.53, 129.10, 128.86, 128.75, 127.62, 127.55, 127.00, 59.97, 58.48, 56.90, 52.24, 49.69, 49.24, 48.24, 47.22, 41.58, 39.36, 38.25, 37.19, 36.08, 35.45, 34.64, 34.43, 24.57, 24.42, 24.25, 20.71, 20.52, 14.56; MS (ESMS) *m/z* 563.3, 565.3 $(M+H)^+$, Cl isotope pattern.

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide; and

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorophenyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide.

The following are non-limiting examples of analogs wherein R^{7a} and R^{7b} are each hydrogen and R^8 units are selected from the group consisiting of phenyl, 2-chlorophenyl, 3-

chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, and naphth-2-yl.

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-{4-[2-(3,4-dichlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

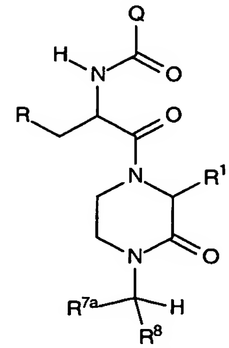
Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(2-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide;

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(3-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide; and

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-{4-[2-(4-chlorobenzyl)-ethyl)-3-oxo-2-cyclopropylmethyl-piperazin-1-yl]-2-oxo-ethyl}-amide.

A further iteration of this aspect comprises compounds having the formula:



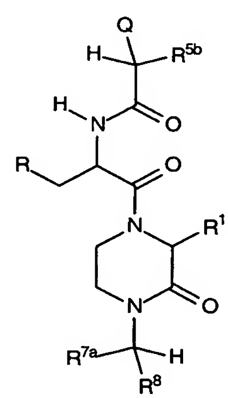
wherein R is a substituted or unsubstituted aryl as defined herein above and non-limiting examples of R^1, R^{7a}, and R^8 are provided herein above in Table IV, said compounds comprising Q units selected from the group consisting of –OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, and $N(CH_3)_2$.

Non-limiting examples of this iteration of aspect two of Category II include:

[2-{4-[2S-(4-Chlorophenyl)-1-isopropylcarbamoyl-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-1R-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester: ^{1}H NMR (MeOH, 300 MHz) δ 7.49-7.38 (m, 2H), 7.33-7.24 (m, 2H), 7.23-7.14 (m, 2H), 7.06-6.92 (m, 2H), 5.44-5.29 (m, 1H), 4.95-4.74 (m, 1H), 4.73 (t, 1H, J=6.62 Hz), 4.07-3.90 (m, 1H), 3.62 (s, 3H), 3.37-2.87 (m, 8H), 1.29-1.04 (m, 8H), 0.89-0.67 (m, 3H); MS (ESI) m/z 623 (M+H$^+$, 100).

[2-{4-[2S-(4-Chlorophenyl)-1-isopropylcarbamoyl-ethyl]-3-oxo-2S-propyl-piperazin-1-yl}-1R-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester: ^{1}H NMR (MeOH, 300 MHz) δ 7.19-7.03 (m, 6H), 6.94-6.80 (m, 2H), 5.26 (q, 2H, J=5.90 Hz), 4.68 (t, 1H, J=7.31 Hz), 4.58 (t, 1H, J=6.65 Hz), 3.94-3.78 (m, 4H), 3.48 (s, 3H), 3.24-2.74 (m, 4H), 1.93 (s, 6H), 1.14-1.03 (m, 2H), 1.01 (q, 2H, J=3.357 Hz), 0.63 (s, 3H); MS (ESI) m/z 589 (M+H$^+$, 100).

A third aspect of Category II comprises analogs with a scaffold having the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{5b}, R^{7a}, R^8 and Q are defined herein below in Table V.

TABLE V

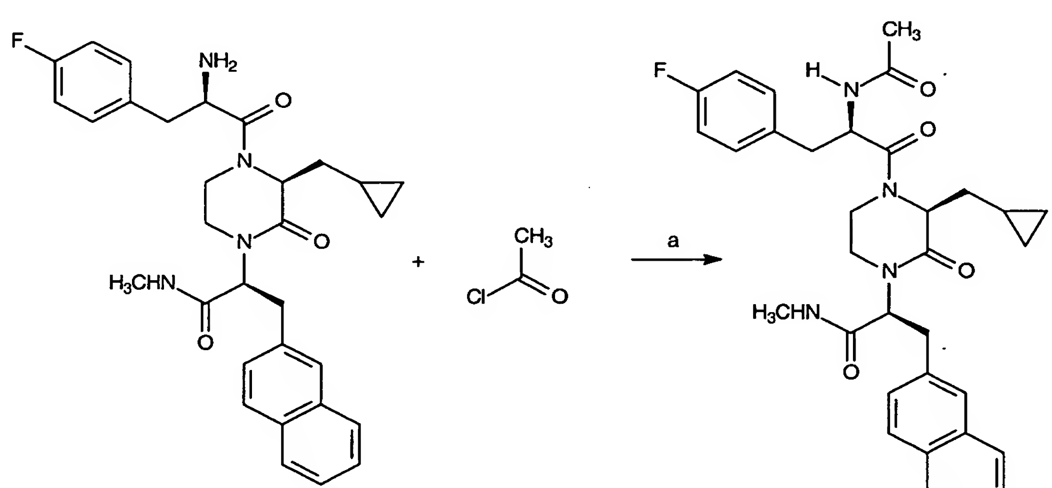
No.	R^1	R^{5b}	Q	R^{7a}	R^8
428	methyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
429	ethyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
430	propyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
431	*iso*-propyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
432	cyclopropyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
433	cyclopropylmethyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
434	allyl	-H	-H	$-C(O)NH_2$	naphthylen-2-ylmethyl
435	methyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
436	ethyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
437	propyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
438	*iso*-propyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
439	cyclopropyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
440	cyclopropylmethyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
441	allyl	-H	$-CH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
442	methyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
443	ethyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
444	propyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
445	*iso*-propyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
446	cyclopropyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
447	cyclopropylmethyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
448	allyl	-H	-H	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
449	methyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
450	ethyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
451	propyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
452	*iso*-propyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
453	cyclopropyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
454	cyclopropylmethyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
455	allyl	-H	$-CH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
456	methyl	-H	-H	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
457	ethyl	-H	-H	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
458	propyl	-H	-H	$-C(O)NHCH_3$	naphthylen-2-ylmethyl

459	*iso*-propyl	-H	-H	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
460	cyclopropyl	-H	-H	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
461	cyclopropylmethyl	-H	-H	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
462	allyl	-H	-H	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
463	methyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
464	ethyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
465	propyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
466	*iso*-propyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
467	cyclopropyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
468	cyclopropylmethyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
469	allyl	-H	-CH$_3$	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
470	methyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
471	ethyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
472	propyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
473	*iso*-propyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
474	cyclopropyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
475	cyclopropylmethyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
476	allyl	-H	-H	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
477	methyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
478	ethyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
479	propyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
480	*iso*-propyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
481	cyclopropyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
482	cyclopropylmethyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
483	allyl	-H	-CH$_3$	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
484	methyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
485	ethyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
486	propyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
487	*iso*-propyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
488	cyclopropyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
489	cyclopropylmethyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
490	allyl	-H	-CH$_3$	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
491	methyl	-H	-H	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
492	ethyl	-H	-H	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
493	propyl	-H	-H	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl
494	*iso*-propyl	-H	-H	-C(O)NH(CH$_2$CH$_2$F)	naphthylen-2-ylmethyl

495	cyclopropyl	-H	-H	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
496	cyclopropylmethyl	-H	-H	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
497	allyl	-H	-H	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
498	methyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
499	ethyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
500	propyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
501	*iso*-propyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
502	cyclopropyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
503	cyclopropylmethyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
504	allyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
505	methyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
506	ethyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
507	propyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
508	*iso*-propyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
509	cyclopropyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
510	cyclopropylmethyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
511	allyl	-H	-CH_3	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl

The compounds which comprise the third aspect of Category II can be suitably prepared according to Scheme VI below from final analogs which comprise Category I, for example, utilizing as starting materials compounds such as **18** which corresponds to analog **9** from Table I.

Scheme VI



18 **24**

Reagents and conditions: (a) TEA, CH_2Cl_2; 0 °C, 3 hr.

EXAMPLE 6

2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide (24)

Preparation of 2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-cyclopropyl-methyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide (24): To a solution of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide, **18**, (100 mg, 0.155 mmol) and triethylamine (20 mg, 0.2 mmole) in CH_2Cl_2 (5 mL) at 0 °C is added dropwise acetyl chloride (13.4 mg, 0.17 mmole). The reaction is allowed to warm to room temperature and stirred 1 hour. The reaction is diluted with CH_2Cl_2 (10 mL) and extracted with water then brine, dried and concentrated in vacuo to afford a residue which is purified over silica gel to afford the desired product. ^{13}C NMR ($CDCl_3$, 75MHz), 170.12, 169.90, 169.82, 169.49, 169.35, 167.70, 134.07, 133.67, 132.57, 131.64, 128.65, 127.83, 127.80, 127.70, 127.51, 127.23, 127.15, 126.64, 126.15, 115.87, 115.79, 115.60, 115.51, 58.65, 57.40, 56.61, 56.43, 50.61, 50.09, 42.76, 41.96, 41.55, 39.84, 38.39, 37.77, 36.89, 34.65, 34.09, 26.59, 23.26, 23.07, 7.20, 7.12, 4.83, 4.69, 4.45; MS, (ES-MS) *m/z* 573 (M+1).

Other non-limiting examples of this aspect of Category II include:

2-{4-[2-Acetylamino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^1H-NMR ($CDCl_3$, 300 MHz) 7.82~7.90 (m, 3H), 7.2~7.55 (m, 6H), 7.00~7.14 (m, 2H), 5.12~5.18 (m, 1H), 2.80~3.45 (m, 8H), 2.60~2.70 (m, 3H), 2.10~2.15 (m, 5H), 1.75~1.90 (m, 3H), 1.59~1.70 (m, 2H), 1.0~1.30 (m, 2H), 0.80~0.90 (m, 3H); MS (ES-MS) *m/z* 547 (M+1).

2-{4-[3-(4-Chlorophenyl)-2-(2-methylamino-acetylamino)-propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^1H NMR ($CDCl_3$, 300 MHz) 7.00~8.00 (m, 11H), 5.01 (m, 1H), 4.64 (t, 1H, *J*=6.6 Hz), 2.60-3.80 (m, 17H), 1.20~1.40 (m, 2H), 0.31 (t, *J*=7.2Hz, 3H); MS (ES-MS) *m/z* 592 (M+1).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-cyclopropyl-3-(S)-naphthalen-2-yl-propionamide: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.71 (m, 3H), 7.56 (s, 1H), 7.51-7.39 (m, 3H), 7.15-7.04 (m, 2H), 6.99-6.88(m, 2H) 6.50 (t, 1H, J=11.67Hz) 6.29 (d, 1H, J=2.37Hz) 5.32 (q, 1H, J=6.70 Hz) 5.04-4.87 (m, 1H) 4.73 (t, 1H, J=6.65 Hz) 3.53-3.14 (m, 4H) 2.97-2.63 (m, 4H) 1.99 (s, 1H) 1.95 (s, 3H) 1.14 (p, 3H, J=18.236 Hz) 0.88-0.58(m, 4H) 0.49 (q, 4H, J=10.755 Hz).

2-{3-Cyclopropylmethyl-4-[3-(R)-(4-fluorophenyl)-2-(S)-(2-methylamino-acetylamino)-propionyl]-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, 1H, J=7.40) 7.78-7.61 (m, 3H) 7.53 (s, 1H) 7.46-7.33 (m, 3H) 7.06 (q, 2H, J=5.33 Hz) 6.97(q, 2H, J=3.14 Hz) 6.91-6.79 (m, 1H) 6.33-6.18 (m, 1H) 5.42 (q, 1H, J=6.86 Hz) 5.29 (q, 1H, J=6.88 Hz) 5.03 (d, 1H, J=7.75 Hz) 4.92 (d, 1H, J=7.49 Hz) 4.73 (t, 1H, 5.32) 3.37-2.94 (m, 2H) 2.60-2.70 (m,2H) 2.63(d, 3H, J=6.07Hz) 1.32-1.21 (m, 1H) 1.08 (d, 2H, J=6.59 Hz) 1.00 (q, 4H, J=6.570 Hz) 0.21-0.18 (m, 4H) MS (ESI) m/z 629 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-butyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.46 (m, 3H) 7.38-7.32 (m, 1H) 7.28-7.17 (m, 2H) 7.09-7.04 (m, 1H) 6.89-6.79 (m, 2H) 6.72-6.64 (m, 2H) 5.13-5.02 (m, 1H) 4.79-4.63 (m, 1H) 4.53 (t, 1H, J=6.64 Hz) 3.47-3.31 (m, 2H) 3.25-2.84 (m, 4H) 2.69-2.46 (m, 4H) 1.67 (s, 3H) 1.26-1.12 (m, 2H) 1.07-0.89 (m, 4H) 0.67-0.58 (m, 3H) 0.53-0.40 (m, 2H) 0.31-0.23 (m, 3H) MS (ESI) m/z 602 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-benzyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78-7.61 (m, 3H) 7.53-7.46 (m, 1H) 7.42-7.32 (m, 2H) 7.16-7.08 (m, 3H) 7.03-6.98 (m, 3H) 6.33-6.25 (m, 1H) 6.00 (d, 1H, J=8.24) 5.32-5.21 (m, 2H) 4.70 (t, 1H, J=6.70 Hz) 4.42-4.08 (m, 2H) 3.61-3.05 (m, 6H) 2.82 (d, 2H, J=7.21 Hz) 1.79 (s, 3H) 1.21-1.08 (m, 2H) 0.73-0.58 (m, 2H) 0.49-0.38 (m, 3H) MS (ESI) m/z 636 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-3-(S)-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69-7.58 (m, 3H) 7.46 (s, 1H) 7.38-7.29 (m, 2H) 7.01-6.89 (m, 3H) 6.84-6.75 (m, 2H) 6.13 (d, 1H, J=8.85 Hz) 5.70 (d, 1H, J=7.29 Hz) 4.98-4.82 (m, 2H) 4.74 (t, 1H, J=5.82 Hz) 3.99-3.83 (m, 2H) 3.78-3.59 (m, 2H) 3.33-3.09 (m, 4H) 2.95-2.72 (m, 2H) 1.75 (s, 3H) 1.48 (s, 6H) 1.06-0.92 (m, 5H) MS (ESI) m/z 600 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-chlorophenyl)-propionyl]-3-(S)-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.52 (m, 3H) 7.43 (s, 1H) 7.36-7.24 (m, 3H) 6.92 (d, 2H, J=19.21 Hz) 6.83 (d, 2H, J=14.83 Hz) 6.07 (d, 1H, J=7.72 Hz) 5.72 (d, 1H, J=6.89 Hz) 5.17-5.09 (m, 2H) 4.69 (t, 1H, J=5.92 Hz) 3.94-3.70 (m, 1H) 3.33-3.01 (m, 4H) 2.92-2.58 (m, 4H) 1.75 (s, 2H) 1.71 (s, 3H) 1.43 (s, 6H) 1.08-0.83 (m, 5H) MS (ESI) m/z 617 (M+H$^+$, 100).

Preparation of 2-{4-[2-Acetylamino-3-(R)-(4-chlorophenyl)-propionyl]-3-(S)-isobutyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.71 (m, 3H) 7.58 (s, 1H) 7.53-7.41 (m, 3H) 7.33-7.19 (m, 2H) 7.10-6.98 (m, 2H) 6.05 (d, 1H, J=8.20 Hz) 5.94 (d, 1H, J=7.75 Hz) 5.37-5.19 (m, 1H) 4.12-3.98 (m, 2H) 3.62-3.49 (m, 1H) 3.38-3.04 (m, 4H) 2.91 (d, 2H, J=7.22 Hz) 2.84-2.74 (m, 2H) 1.94 (s, 1H) 1.89 (s, 2H) 1.18-1.04 (m, 6H) MS (ESI) m/z 618 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-chlorophenyl)-propionyl]-3-(S)-isopropyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82-7.71 (m, 3H) 7.58 (s, 1H) 7.49-7.41 (m, 2H) 7.28-7.18 (m, 3H) 7.14-7.06 (m, 2H) 6.07-5.94 (m, 2H) 5.14-4.99 (m, 1H) 5.09-4.99 (m, 1H) 4.68 (d, 1H, J=7.050 Hz) 4.08-3.96 (m, H) 3.78-3.57 (m, 2H) 3.49-3.21 (m, 4H) 3.09-2.84 (m, 2H) 2.76-2.68 (m, 1H) 1.86 (s, 3H) 1.64 (s, 6H) 1.09 (t, 6H, J=6.577 Hz) MS (ESI) m/z 605 (M+H$^+$, 100).

2-Amino-N-[2-[2-(S)-cyclopropylmethyl-4-(1-isopropylcarbamoyl-2-(S)-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1R-(4-fluorobenzyl)-2-oxo-ethyl]-2-ethyl-butyramide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.67 (m, 3H) 7.58 (s, 1H) 7.49-7.38 (m, 2H) 7.22-7.12 (m, 1H) 7.08-7.00 (m, 1H)6.99-6.87 (m, 3H) 6.32 (t, 1H, J=9.62 Hz) 5.5 (q, 1H, J=6.23 Hz) 5.38 (q, 1H, J=6.89 Hz) 4.81 (t, 1H, J=5.31 Hz) 4.11-3.89 (m, 1H) 3.61-3.04 (m, 4H) 3.00-2.91 (m, 2H) 2.89-2.78 (m, 2H) 2.03-1.74 (m, 6H) 1.42-1.30 (m, 1H) 1.22-0.98 (m, 6H) 0.95-0.75 (m, 6H) 0.10-0.03 (m, 5H) MS (ESI) m/z 671 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-3-(S)-(1H-indol-2-yl)-N-methyl-propionamide: ^{1}H NMR ($CDCl_3$,300 MHz) δ. 8.21 (s, 1H), 7.56 (d, 1H, J=7.72 Hz), 7.49-6.86 (m, 8H), 6.47 (d, 1H, J=8.02 Hz), 5.37-5.24 (m, 1H), 5.02-4.91 (m, 1H), 4.79 (t, 1H, J=6.53 Hz), 3.32-3.08 (m, 4H), 2.93 (d, 2H, J=7.31 Hz), 2.84 (d, 2H, J=4.76 Hz), 2.76 (d, 3H, J=4.61 Hz), 1.95 (s, 3H), 1.39-1.22 (m, 2H), 0.94-0.80 (m, 2H), 0.78-0.68 (m, 3H).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.68 (m, 3H), 7.56 (s, 1H), 7.52-7.41 (m, 2H), 7.16-6.88 (m, 5H), 6.37-6.20 (m, 1H), 6.01-5.80 (m, 1H), 5.34-5.23 (m, 1H), 5.03-4.72 (m, 2H), 4.16-3.94 (m, 1H), 3.50-3.07 (m, 4H), 2.91 (d, 2H, J=7.50 Hz), 2.85 (d, 2H, J=6.95 Hz), 1.92 (s, 3H), 1.18-1.02 (m, 10H), 0.54-0.45 (m, 3H); MS (ESI) m/z 589 (M+H$^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-3-(S)-isobutyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.70 (m, 3H) 7.56 (s, 1H) 7.52-7.40 (m, 2H) 7.14-7.02 (m, 3H) 6.98-6.86 (m, 2H) 6.05 (d, 1H, J=8.30 Hz) 5.94 (d, 1H, J=7.57 Hz) 5.35-5.20 (m, 2H) 5.00-4.82 (m, 1H) 4.10-3.85 (m, 1H) 3.58-3.05 (m, 4H) 2.94-2.83 (m, 2H) 2.79-2.68 (m, 2H) 1.88 (s, 3H) 1.61 (s, 6H) 1.17-0.59 (m, 9H) MS (ESI) m/z 603 ($M+H^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-3-(S)-isopropyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82-7.70 (m, 3H) 7.58 (s, 1H) 7.49-7.41 (m, 2H) 7.17-7.08 (m, 2H) 7.02-6.88 (m, 3H) 6.29 (d, 1H, J=7.65 Hz) 6.03 (t, 1H, J=9.05 Hz) 5.34-5.19 (m, 1H) 5.09-4.98 (m, 1H) 4.67 (d, 1H, J=6.97 Hz) 4.24-3.93 (m, 2H) 3.78-3.53 (m, 2H) 3.41-3.13 (m, 2H) 3.09-2.69 (m, 2H) 2.02-1.83 (m, 4H) 1.66 (s, 6H) 1.12-1.02 (m, 6H) MS (ESI) m/z 589 ($M+H^+$, 100).

Cyclopropanecarboxylic acid [2-[2-(S)-cyclopropylmethyl-4-(S)-(1-isopropyl-carbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(R)-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.812-7.68 (m, 3H) 7.58 (s, 1H) 7.52-7.39 (m, 3H) 7.34-7.28 (m, 2H) 7.14-7.01 (m, 2H) 6.97-6.87 (m, 2H) 6.18 (d, 1H, J=8.36 Hz) 5.86 (d, 1H, J=7.37) 5.12-4.95 (m, 1H) 4.87 (t, 1H, J=5.87) 4.10-3.92 (m, 1H) 3.84-3.70 (m, 1H) 3.42-2.97 (m, 4H) 3.05-2.94 (m, 2H) 2.90-2.79 (m, 2H) 1.73 (s, 8H) 1.24-1.02 (m, 5H) 0.92-0.81 (m, 1H) 0.78-0.66 (m, 2H) MS (ESI) m/z 627 ($M+H^+$, 100).

2-{4-[2-Acetylamino-3--(R)-(4-chlorophenyl)-propionyl]-3-(S)-cyclohexylmethyl-2-oxo-piperazin-1-yl}-N-isopropyl-3S-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82-7.70 (m, 3H) 7.58 (s, 1H) 7.54-7.39 (m, 2H) 7.36-7.19 (m, 3H) 7.12-7.05 (m, 2H) 6.06 (d, 1H, J=8.17 Hz) 5.97 (d, 1H, J=7.55 Hz) 5.36-5.17 (m, 2H) 5.00-4.84 (m, 1H) 4.10-3.92 (m, 1H) 3.39-3.02 (m, 4H) 2.91 (d, 2H, J=7.13 Hz) 2.88-2.75 (m, 2H) 1.87 (s, 3H) 1.73-1.40 (m, 11H) 1.18-0.87 (m, 11H) MS (ESI) m/z 660 ($M+H^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-3-(S)-butyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75-6.70 (m, 11H) 6.14 (d, 1H, J=7.56 Hz) 5.94 (d, 1H, J=8.13 Hz) 5.29-5.10 (m, 1H) 4.95-4.60 (m, 2H) 4.09-3.82 (m, 1H) 3.60-3.04 (m, 4H) 2.91-2.58 (m, 4H) 1.89-1.41 (m, 5H) 1.22-0.46 (m, 13H) MS (ESI) m/z 603($M+H^+$, 100).

2-{4-[2-Acetylamino-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-3-(S)-propyl-piperazin-1-yl}-N-methyl-3-(S)--naphthalen-1-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04-6.70

(m, 11H) 6.65 (d, 1H, J=11.0 Hz) 6.34 (d, 1H, J=8.21 Hz) 5.46-5.32 (m, 1H) 5.01-4.88 (m, 1H) 4.62 (t, 1H, J=6.86 Hz) 3.70-3.42 (m, 4H) 3.32-3.12 (m, 4H) 2.92 (d, 3H, J=7.74 Hz) 2.86-2.72 (m, 3H) 2.66 (d, 2H, J=4.60 Hz) 1.28-0.78 (m, 4H).

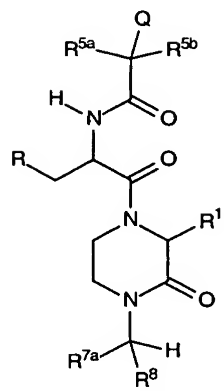
2-{3-(S)-Cyclopropylmethyl-4-[3-(R)-(4-fluorophenyl)-2-(2-methoxy-acetylamino)-propionyl]-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80-7.68 (m, 3H) 7.58 (s, 1H) 7.48-7.41 (m, 2H) 7.17-7.05 (m, 3H) 6.98-6.88 (m, 2H) 5.89 (t, 2H, J=9.03 Hz) 5.44 (q, 1H, J=12.67 Hz) 5.32-5.23 (m, 1H) 5.11-5.01 (m, 2H) 4.86 (t, 1H, J=5.82 Hz) 4.12-3.98 (m, 2H) 3.87-3.72 (m, 2H) 3.37 (d, 3H, J=7.07 Hz) 3.08-2.98 (m, 2H) 2.91-2.82 (m, 2H) 2.04 (s, 6H) 1.41-1.29 (m, 2H) 1.17 (d, 4H, J=6.083 Hz) 1.09 (t, 1H, J= 5.435 Hz) MS (ESI) m/z 630 (M+H$^+$, 100).

2-{3-(S)-Cyclopropylmethyl-4-[2-(2,2-difluoro-acetylamino)-3-(R)-(4-fluorophenyl)-propionyl]-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.68 (m, 3H) 7.58(s, 1H) 7.49-7.41 (m, 2H) 7.14-7.02 (m, 3H) 6.98-6.89 (m, 2H) 5.98(d, 1H, J=1.22 Hz) 5.81 (d, H, J=1.09 Hz) 5.63 (d, 1H, J=1.06 Hz) 5.38 (q, 1H, J=6.63 Hz) 5.28 (q, 1H, J=7.00 Hz) 5.12-4.93 (m, 1H) 4.84 (t, 1H, J=5.96 Hz) 3.54-3.15 (m, 4H) 3.07-2.98 (m, 2H) 2.97-2.84 (m, 2H) 1.16 (d, 2H, J=6.552 Hz) 1.08 (t, 6H, J=5.804 Hz) 0.18-0.12 (m, 5H) MS (ESI) m/z 636 (M+H$^+$, 100)

2-{4-[2-(2-Cyano-acetylamino)-3-(R)-(4-fluorophenyl)-propionyl]- 3-(S)-cyclopropyl-methyl-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76-7.58 (m, 3H) 7.53 (s, 1H) 7.44-7.30 (m, 3H) 7.28-7.18 (m, 2H) 7.03(q, 2H, J=5.31 Hz) 6.95-6.78 (m, 1H) 6.28(d, 1H, J=7.72 Hz) 6.18 (d, 1H, J=7.56 Hz) 5.45 (q, 1H, J=6.84 Hz) 5.12-4.98 (m, 1H) 4.72 (t, 1H, J=5.55 Hz) 3.94-3.77 (m, 2H) 3.48-2.65 (m, 6H) 1.49(s, 6H) 1.38 (s, 6H) 1.05 (t, 1H, J=6.552 Hz) 0.97 (q, 4H, J=3.723 Hz) MS (ESI) m/z 643 (M+H$^+$, 100).

2-{3-Cyclopropylmethyl-4-[3-(R)-(4-fluorophenyl)-2S-(2-methylamino-acetylamino)-propionyl]-2-oxo-piperazin-1-yl}-N-isopropyl-3-(S)-naphthalen-2-yl-propionamide: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, 1H, J=7.40) 7.78-7.61 (m, 3H) 7.53 (s, 1H) 7.46-7.33 (m, 3H) 7.06 (q, 2H, J=5.33 Hz) 6.97(q, 2H, J=3.14 Hz) 6.91-6.79 (m, 1H) 6.33-6.18 (m, 1H) 5.42 (q, 1H, J=6.86 Hz) 5.29 (q, 1H, J=6.88 Hz) 5.03 (d, 1H, J=7.75 Hz) 4.92 (d, 1H, J=7.49 Hz) 4.73 (t, 1H, 5.32) 3.37-2.94 (m, 2H) 2.60-2.70 (m,2H) 2.63(d, 3H, J=6.07Hz) 1.32-1.21 (m, 1H) 1.08 (d, 2H, J=6.59 Hz) 1.00 (q, 4H, J=6.570 Hz) 0.21-0.18 (m, 4H) MS (ESI) m/z 629 (M+H$^+$, 100).

The fourth aspect of Category II comprises analogs with a scaffold having the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^4, R^{5b}, R^8 and Q are defined herein below in Table VI.

TABLE VI

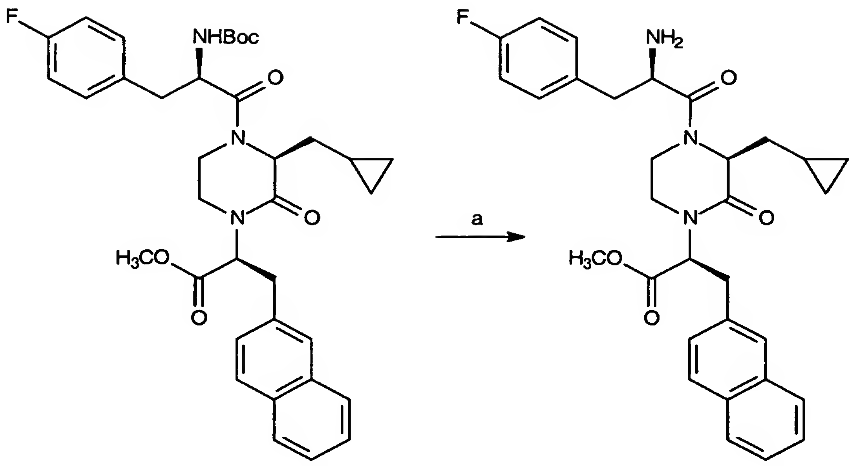
No.	R^1	R^{7a}	R^{5a}	R^{5b}	Q	R^8
511	methyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
512	ethyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
513	propyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
514	*iso*-propyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
515	cyclopropyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
516	cyclopropylmethyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
517	allyl	$-CO_2H$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
518	methyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
519	ethyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
520	propyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
521	*iso*-propyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
522	cyclopropyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
523	cyclopropylmethyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
524	allyl	$-CO_2H$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
525	methyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
526	ethyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
527	propyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
528	*iso*-propyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
529	cyclopropyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
530	cyclopropylmethyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
531	allyl	$-CO_2H$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
532	methyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl

533	ethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
534	propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
535	*iso*-propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
536	cyclopropyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
537	cyclopropylmethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
538	allyl	$-CO_2CH_3$	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
539	methyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
540	ethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
541	propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
542	*iso*-propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
543	cyclopropyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
544	cyclopropylmethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
545	allyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(3,4-dichlorphenyl)methyl
546	methyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
547	ethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
548	propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
549	*iso*-propyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
550	cyclopropyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
551	cyclopropylmethyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
552	allyl	$-CO_2CH_3$	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
553	methyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
554	ethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
555	propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
556	*iso*-propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
557	cyclopropyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
558	cyclopropylmethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
559	allyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
560	methyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
561	ethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
562	propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
563	*iso*-propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
564	cyclopropyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
565	cyclopropylmethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
566	allyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
567	methyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
568	ethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl

569	propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
570	*iso*-propyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
571	cyclopropyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
572	cyclopropylmethyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
573	allyl	$-CO_2H$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
574	methyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
575	ethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
576	propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
577	*iso*-propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
578	cyclopropyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
579	cyclopropylmethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
580	allyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
581	methyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
582	ethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
583	propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
584	*iso*-propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
585	cyclopropyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
586	cyclopropylmethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(3,4-dichlorphenyl)methyl
587	methyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
588	ethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
589	propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
590	*iso*-propyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
591	cyclopropyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
592	cyclopropylmethyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
593	allyl	$-CO_2CH_3$	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl

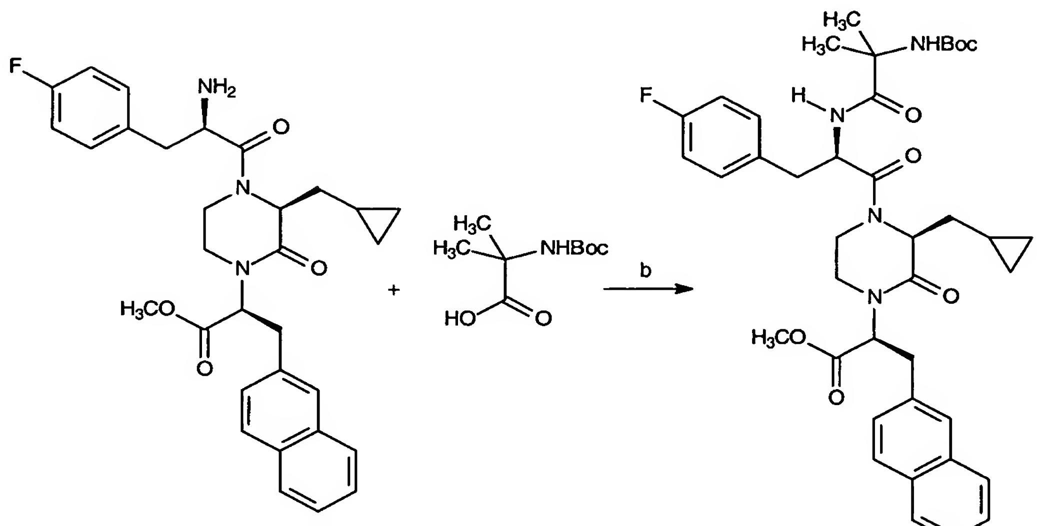
The compounds which comprise the fourth aspect of Category II can be suitably prepared starting with intermediate compounds such as **15** as outlined in Scheme VII herein below.

Scheme VII



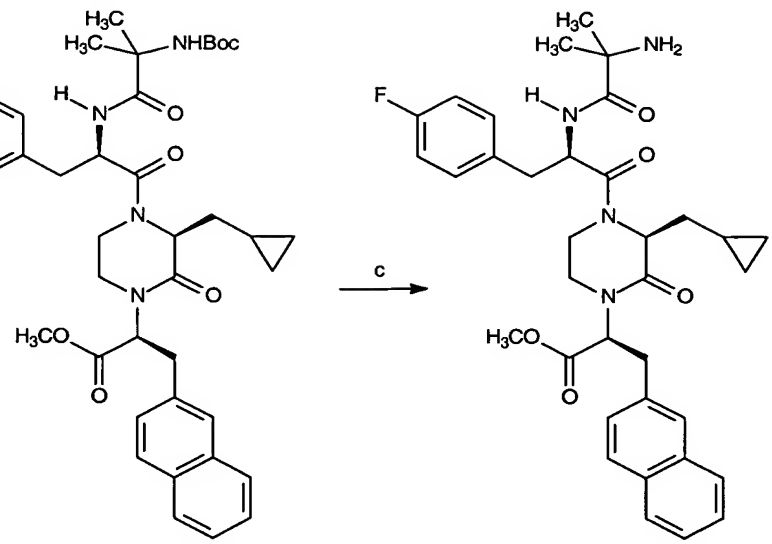
15 **25**

Reagents and conditions: (a) TFA/anisole/CH_2Cl_2; rt, 3 minutes.



25 **26**

Reagents and conditions: (b) EDCI, HOBt, NMM; rt, 3 hr.



26 27

Reagents and conditions: (c) TFA/anisole/CH_2Cl_2; rt, 3 minutes.

EXAMPLE 7

2-{4-[2-(2-Amino-2-mmethyl-propionylamino)-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (27)

Preparation of 2-{4-[2-amino-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methylester (25): To a solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **15**, (531 mg, 0.842 mmol) is dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 10 mL). The reaction mixture was stirred for 3 minutes, concentrated *in vacuo* and the residue purified by reverse phase HPLC to afford the TFA salt of the desired compound.

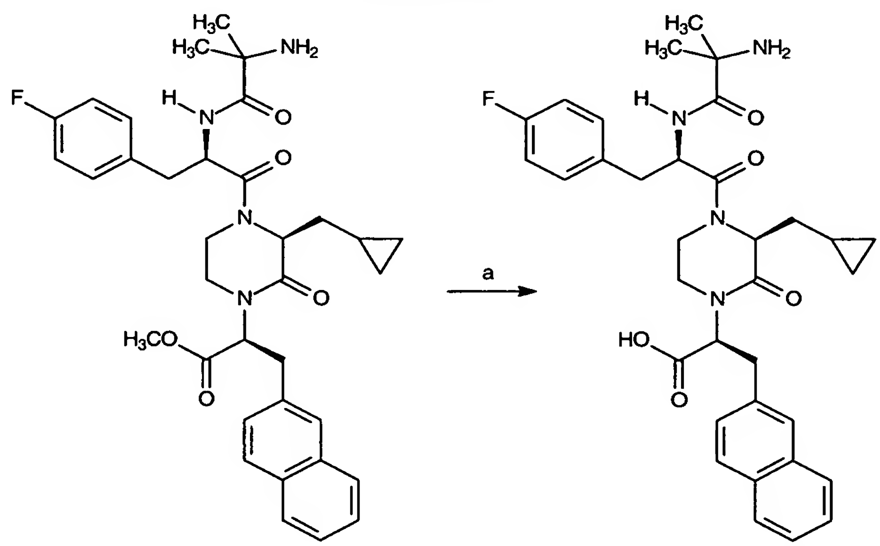
Preparation of 2-{4-[2-(2-*tert*-butoxycarbonylamino-2-methyl-propionylamino)-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methylester (26): To a solution of 2-{4-[2-amino-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methylester, **25**, (37 mg, 0.068 mmol) in DMF (1 mL) are added 2-*tert*-butoxycarbonylamino-2-methyl-propionic acid (202 mg, 0.079 mmol), 1-hydroxybenzotriazole (20 mg, 0.148 mmol), N-methylmorpholine (41 mg, 0.41 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (16 mg, 0.083 mmol) consecutively. The reaction mixture is stirred for 3 hours, quenched with aqueous NH_4Cl and extracted several times with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated

in vacuo to a residue which is purified over silica gel (CH_2Cl_2/CH_3OH, 13:1) to afford the desired product.

Preparation of 2-{4-[2-(2-amino-2-mmethyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (27): To a solution of 2-{4-[2-(2-*tert*-butoxycarbonylamino-2-methyl-propionyl-amino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **26**, (45 mg, 0.063 mmol) is dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 2 mL). The reaction mixture is stirred for 3 minutes, concentrated *in vacuo* and the residue purified by reverse phase HPLC to afford the TFA salt of the desired compound.

A further iteration of the fourth aspect of Category II relates to R^{7a} units which are carboxy, which can be prepared from the corresponding esters as outlined in Scheme VIII.

Scheme VIII



27 **28**

Reagents and conditions: (a) LiOH, THF/MeOH/H_2O; rt, 4 hr.

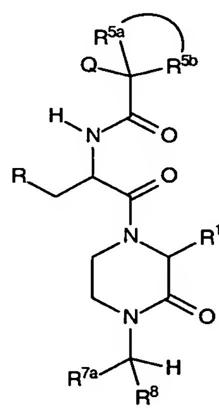
EXAMPLE 8

<u>2-{4-[2-(2-Amino-2-mmethyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (28)</u>

Preparation of 2-{4-[2-(2-amino-2-mmethyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (28):

To a solution of 2-{4-[2-(2-amino-2-mmethyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **27**, (518 mg, 0.842 mmol) in a mixture of THF (5mL)/CH_3OH (1 mL)/H_2O (2 mL) is added LiOH (100 mg, 4.17 mmol). The reaction mixture is stirred for 4 hours, acidified with 1N HCl to pH 3 and extracted several times with EtOAc. The combined extracts are dried over Na_2SO_4, filtered, concentrated *in vacuo* and dried under high vacuum to give the free acid in quantitative yield.

A fifth aspect of Category II melanocortin receptor ligands relate to compounds wherein R^{5a} and R^{5b} are taken together to form a carbocyclic or heterocyclic ring having from 3 to 10 atoms, said compounds having the general scaffold with the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{5a}/R^{5b} ring, R^{7a}, R^8 and Q are defined herein below in Table VII. 1,2,3,4-THN-2-yl stands for 1,2,3,4-tetrahydronaphthylen-2-yl.

TABLE VII

No.	R^1	R^{5a}/R^{5b} ring	Q	R^{7a}	R^8
594	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
595	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
596	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
597	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
598	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
599	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
600	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
601	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
602	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
603	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl

604	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
605	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
606	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
607	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
608	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
609	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
610	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
611	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
612	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
613	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
614	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
615	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
616	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
617	$-CH_2CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
618	$-CH_2CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
619	$-CH_2CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
620	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
621	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
622	$-CH_2(C_3H_5)$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
623	$-CH_2(C_3H_5)$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
624	$-CH_2(C_3H_5)$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
625	$-CH_2(C_3H_5)$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
626	$-CH_2(C_3H_5)$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
627	$-CH_2(C_3H_5)$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
628	$-CH_2(C_3H_5)$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
629	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
630	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
631	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
632	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
633	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
634	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
635	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
636	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
637	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
638	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
639	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl

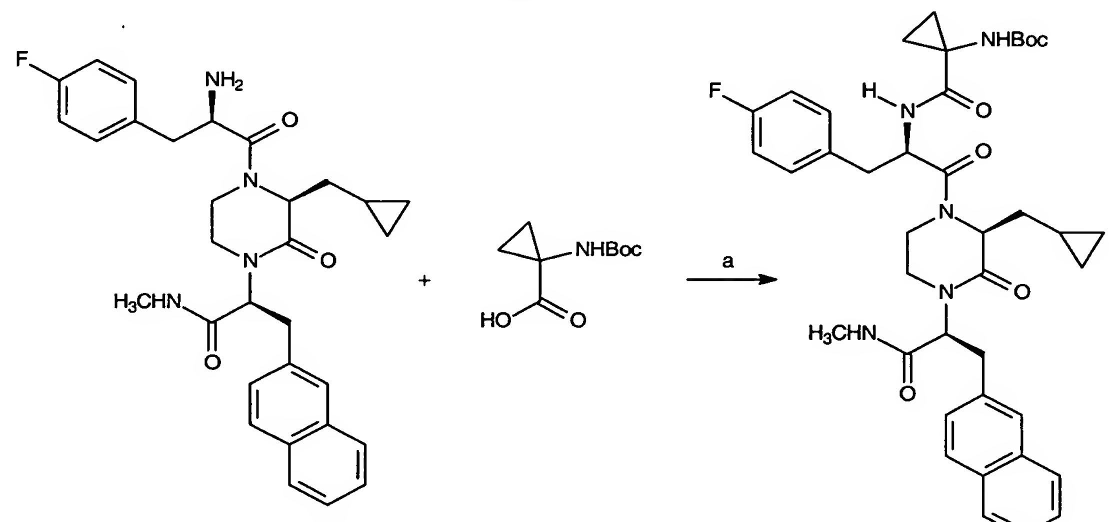
640	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
641	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
642	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
643	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
644	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
645	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
646	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
647	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
648	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
649	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
650	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
651	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
652	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
653	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
654	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
655	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
656	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
657	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
658	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
659	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
660	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
661	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
662	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
663	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
664	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
665	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
666	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
667	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
668	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
669	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
670	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
671	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
672	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
673	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
674	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
675	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl

676	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
677	$-CH_2CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
678	$-CH_2CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
679	$-CH_2CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
680	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
681	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
682	$-CH_2(C_3H_5)$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
683	$-CH_2(C_3H_5)$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
684	$-CH_2(C_3H_5)$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
685	$-CH_2(C_3H_5)$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
686	$-CH_2(C_3H_5)$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
687	$-CH_2(C_3H_5)$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
688	$-CH_2(C_3H_5)$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3.4-dichlorophenyl)methyl
689	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
690	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
691	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
692	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
693	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
694	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
695	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
696	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
697	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
698	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
699	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
700	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
701	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
702	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
703	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
704	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
705	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
706	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
707	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
708	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
709	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
710	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
711	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl

712	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl
713	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3.4-dichlorophenyl)methyl

The compounds which comprise the fifth aspect of Category II melanocortin receptor ligands can be suitably prepared starting with intermediate compound **18** as outline in Scheme IX herein below.

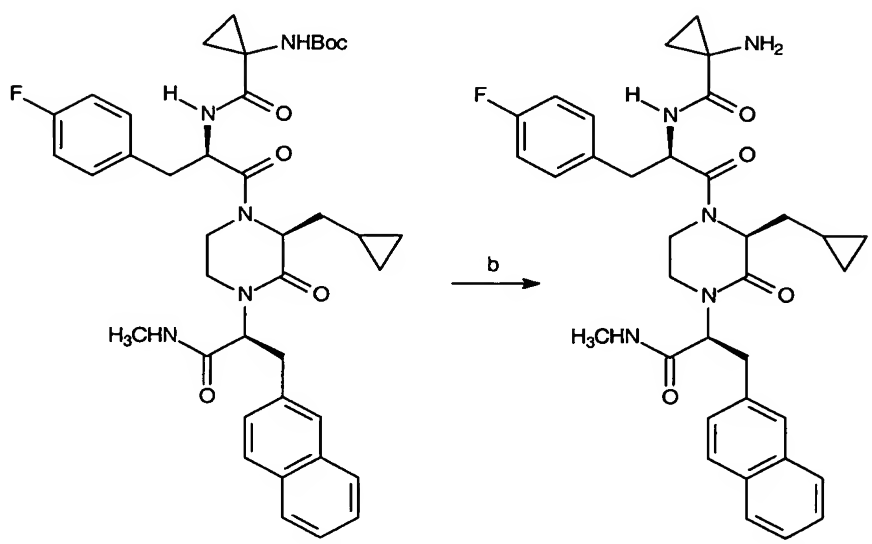
Scheme IX



18

29

Reagents and conditions: (a) EDCI, HOBt, NMM; rt, 3 hr.



29 **30**

Reagents and conditions: (b) TFA/anisole/CH_2Cl_2; rt, 1 hr.

EXAMPLE 9

1-Amino-cyclopropane carboxylic acid [2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-ylethyl)piperazin-1-yl]-1-(4fluorobenzyl)-2-oxo-ethyl]-amide (30)

Preparation of {1-[2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-ylethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]cyclopropyl}-carbamic acid tert-butyl ester (29): To a solution of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide, **18**, (62 mg, 0.12 mmol) in DMF (2 mL) are added *tert*-butoxycarbonylamino-cyclopropanecarboxylic acid (28.5 mg, 0.14 mmol), 1-hydroxybenzotriazole (36 mg, 0.266 mmol), N-methylmorpholine (74 mg, 0.74 mmol) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (29 mg, 0.15 mmol) consecutively. The reaction mixture is stirred for 3 hours, quenched with aqueous NH_4Cl and extracted several times with ethyl acetate. The combined extracts are dried over Na_2SO_4, filtered and concentrated in vacuo to a residue, which is purified over silica gel (CH_2Cl_2/CH_3OH, 13:1) to afford the desired product.

Preparation of 1-amino-cyclopropane carboxylic acid [2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-ylethyl)piperazin-1-yl]-1-(4fluorobenzyl)-2-oxo-ethyl]-amide (30): {1-[2-[2-cyclopropylmethyl-4-(1-methylcarbamoyl-2-naphthalen-2-ylethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]cyclopropyl}-carbamic acid tert-butyl ester, **29**, (63 mg, 0..09 mmol) was dissolved into a mixture of TFA/anisole/CH_2Cl_2 (45:5:50, 2 mL). The reaction mixture is stirred for 1 hour, concentrated *in vacuo* and the residue purified by reverse phase HPLC purification to afford the TFA salt of the desired compound.

N-[2-{4-[2-(4-Chlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide HCl: ^1H NMR (CD_3OD, with rotamers) δ 9.01 (br s, 2H), 8.32 (d, 2H, J = 5.7 Hz), 7.39-7.31 (m, 6H), 7.04 (m, 2H), 5.44 (m, 1H), 5.31 (m, 1H), 4.75 (m, 1H), 4.05 (m, 1H), 3.77-3.51 (m, 2H), 3.30-3.00 (m, 5H), 2.83, 2.74 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 1.44-0.83 (m, 7H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.0, 171.9, 171.4, 171.3, 170.7, 169.0, 165.0, 164.4, 162.8, 150.6, 145.0, 137.1, 137.0, 133.9, 133.7, 133.5, 133.3, 132.6, 132.5, 132.1, 132.0, 131.7, 129.8, 126.5, 126.0, 116.8, 116.7, 116.5, 116.4, 73.7, 72.6, 62.3, 59.8, 58.0, 57.4, 53.4, 52.8, 49.7, 48.1, 43.9, 43.3, 42.7, 42.6, 39.5, 38.8, 38.1, 36.7, 35.5, 35.3, 34.7, 26.6, 20.2, 20.0, 19.7, 14.3, 9.4; MS *m/z* (ESI): 608 (M + H, 60), 610 (M + 2 + H, 20), 630 (M + Na + H, 100).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoro-acetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.26 (m, 6H), 7.03 (m, 2H), 5.48 (m, 1H), 5.06 (m, 1H), 4.67 (m, 1H), 3.99 (m, 1H), 3.61 (m, 1H), 3.26-2.93 (m, 6H), 2.80, 2.74 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 1.62 (m, 1H), 1.39-1.20 (m, 5H), 0.79 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.9, 171.7, 171.5, 170.7, 170.5, 169.0, 164.2, 162.6, 162.5, 136.8, 133.8, 133.6, 132.3, 131.9, 131.8, 129.6, 116.6, 116.5, 116.3, 116.2, 59.6, 57.5, 57.4, 57.2, 52.6, 52.1, 42.9, 42.5, 39.3, 38.3, 37.6, 36.5, 36.3, 35.5, 35.0, 34.8, 26.4, 20.1, 19.8, 14.2, 13.5, 13.3, 13.2; MS *m/z* (ESI): 586 (M + H, 80), 588 (M + 2 + H, 28), 338 (100).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.16 (m, 6H), 6.90 (m, 2H), 5.36 (m, 1H), 4.98 (m, 1H), 4.55 (m, 1H), 3.88 (m, 1H), 3.48 (m, 1H), 3.15-2.83 (m, 6H), 2.68, 2.62 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.58, 2.55 (2 singlets, 3H, $CH_3NHC(CH_2$-$CH_2)C(O)$, rotamers), 1.52 (m, 1H), 1.36 (m, 3H), 1.11 (m, 2H), 0.68 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.9, 171.8, 171.6, 171.4, 170.5, 169.5, 164.2, 162.6, 162.4, 162.1, 136.8, 133.8, 133.7, 132.4, 132.3, 131.9, 131.8, 129.6, 116.6; 116.4, 116.3, 116.1, 59.7, 57.4, 57.2, 52.6, 52.0, 43.6, 43.0, 42.5, 39.2, 38.3, 37.6, 36.5, 35.5, 35.0, 34.8, 32.8, 32.7, 26.4, 20.1, 19.8, 14.2, 13.4, 13.2; MS *m/z* (ESI): 600 (M + H, 80), 602 (M + 2 + H, 37).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(2,4-dichlorophenyl)-1-methyl-carbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.28 (m, 1H), 7.11 (m, 4H), 6.87 (m, 2H), 5.43 (m, 1H), 4.92 (m, 1H), 4.53 (m, 1H), 3.88 (m, 1H), 3.38 (m, 1H), 3.26-3.06 (m, 3H), 2.83 (m, 3H), 2.63, 2.58 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 1.45 (m, 1H), 1.23-1.17 (m, 5H), 0.65 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.7, 171.5, 171.3, 171.2, 170.7, 170.4, 168.9, 164.2, 162.7, 162.6, 162.5, 136.4, 136.3, 134.8, 134.7, 133.9, 133.7, 133.6, 133.5, 132.3, 131.9, 130.3, 128.4, 119.0, 116.5, 116.4, 116.3, 116.2, 134.1, 1332.7, 132.6, 132.3, 130.7, 128.8, 117.0, 116.8, 116.5, 59.6, , 57.1, 56.0, 52.6, 52.1, 43.3, 42.9, 42.3, 38.9, 38.2, 37.6, 36.6, 36.3, 35.4, 32.7, 32.3, 26.5, 20.1, 19.9, 14.2, 13.6, 13.4, 13.3; MS *m/z* (ESI): 620 (M + H, 60), 602 (M + 2 + H, 40).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(2,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-3-oxo-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.22 (m, 1H), 7.04 (m, 4H), 6.81 (m, 2H), 5.35 (m, 1H), 4.88 (m, 1H), 4.46 (m, 1H), 3.76 (m, 1H), 3.29-3.00 (m, 4H), 2.77 (m, 3H),

2.73, 2.57 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.51, 2.46 (2 singlets, 3H, $CH_3NHC(CH_2$-$CH_2)C(O)$, rotamers), 1.41 (m, 1H), 1.25 (m, 3H), 1.08 (m, 2H), 0.59 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.0, 171.0, 170.0, 165.5, 162.2, 136.7, 135.2, 135.1, 134.1, 132.8, 132.7, 130.7, 128.8, 116.8, 116.5, 60.1, 57.5, 56.5, 52.9, 52.4, 44.143.8, 42.7, 38.1, 37.0, 35.9, 33.3, 32.7, 26.9, 20.5, 20.3, 14.6, 13.8; MS *m/z* (ESI): 634 (M + H, 100), 606 (M + 2 + H, 70).

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^1H NMR ($CDCl_3$, 300 MHz) 7.00~8.00 (m, 11H), 4.57 (m, 1H), 4.10~4.30 (m, 2H), 2.60~3.75 (m, 12H), 1.85 (bs, 2H), 1.25~1.50 (m, 2H), 0.40~0.60 (m, 3H); MS (ES-MS) *m/z* 592 (M+1).

The following are non-limiting examples of analogs according to Category II of the melanocortin receptor ligands of the present invention.

N-(2-Fluoroethyl)-2-{4-[3-(4-fluorophenyl)-2-methylamino-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide: ^1H NMR (300 MHz, MeOD, Rotamers) δ 8.38-8.86 (m, 0.3H), 7.77-7.89 (m, 3H), 7.62-7.72 (m, 1H), 7.38-7.58 (m, 3H), 7.15-7.30 (m, 2H), 6.94-7.11 (m, 2H), 5.52-5.65 (m, 1H), 4.20-4.68 (m, 4H), 3.16-3.68 (m, 8H), 2.56-3.04 (m, 5H), 0.72-1.14 (m, 2H), 0.18-0.66 (m, 5H); ^{13}C NMR (75 MHz, MeOD, Rotamers) δ 172.23, 169.85, 167.14, 162.39, 135.65, 135.03, 134.10, 132.90, 132.79, 130.66, 129.45, 128.91, 128.83, 128.63, 128.32, 127.57, 127.04, 117.10, 116.81, 84.29, 82.07, 59.79, 58.32, 57.87, 43.58, 42.84, 41.42, 41.14, 39.31, 37.13, 36.63, 35.69, 35.47, 32.34, 19.78, 13.86; MS (ESMS) *m/z* 565.4 $(M+H)^+$.

N-(2-Fluoroethyl)-2-{4-[3-(4-fluorophenyl)-2-isopropylamino-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide: ^1H NMR (300 MHz, CD_3OD, Rotamers) δ 8.36-8.46 (m, 0.6H), 7.70-7.92 (m, 3H), 7.34-7.65 (m, 4H), 7.16-7.33 (m, 2H), 6.94-7.10 (m, 2H), 5.57 (dd, J = 12.3, 5.1 Hz, 1H), 4.71 (dd, J = 10.8, 5.1 Hz, 1H), 4.46-4.60 (m, 2H), 4.32-4.44 (m, 1H), 3.36-3.37 (m, 5H), 3.09-3.32 (m, 4H), 2.90-3.04 (m, 1H), 2.50-2.64 (m, 1H), 1.23-1.36 (m, 6H), 0.60-1.14 (m, 2H), 0.14-0.58 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 172.49, 170.00, 167.27, 165.92, 162.65, 135.88, 135.28, 134.36, 133.28, 133.18, 132.65, 132.54, 130.90, 129.71, 129.18, 129.04, 128.88, 128.54, 127.85, 127.32, 117.81, 117.30, 117.01, 84.56, 82.34, 58.54, 58.36, 56.22, 51.53, 43.77, 43.26, 41.67, 41.40, 38.02, 35.96, 35.77, 20.62, 20.02, 19.24, 14.10; MS (ESMS) *m/z* 593.3 $(M+H)^+$.

2-{4-[2-Ethylamino-3-(4-fluorophenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-N-(2-fluoroethyl)-3-naphthalen-2-yl-propionamide: ^1H NMR (300 MHz, CD_3OD, Rotamers) δ 8.60-8.70 (m, 0.15H), 8.37-8.48 (m, 0.75H), 7.75-7.89 (m, 3H), 7.61-7.74 (m, 1H), 7.36-7.59 (m,

3H), 7.14-7.30 (m, 2H), 6.94-7.11 (m, 2H), 5.60 (dd, J = 11.8, 5.0 Hz, 1H), 4.17-4.72 (m, 4H), 3.12-3.70 (m, 7H), 2.74-3.08 (m, 3H), 2.50-2.64 (m, 1H), 1.30 (t, J = 7.4 Hz, 3H), 0.12-1.16 (m, 7H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 172.48, 170.06, 168.18, 167.47, 165.91, 163.15, 162.65, 135.85, 135.28, 134.37, 133.16, 133.06, 132.56, 132.46, 131.03, 130.99, 129.69, 129.16, 129.06, 128.87, 128.56, 127.82, 127.30, 117.83, 117.55, 117.34, 117.05, 84.55, 82.34, 59.48, 59.35, 58.64, 58.32, 58.20, 57.36, 43.57, 43.34, 43.21, 41.67, 41.39, 39.72, 37.81, 37.63, 37.01, 35.97, 35.74, 20.00, 14.10, 12.07; MS (ESMS) *m/z* 579.3 $(M+H)^+$.

2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-methyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-chlorophenyl)propionyl]-3-methyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-chlorophenyl)propionyl]-3-ethyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-propyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

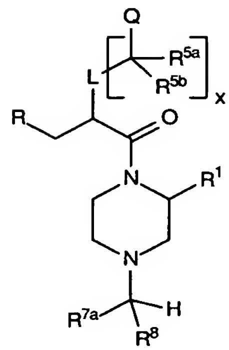
2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-cyclopropylmethyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-(1-methylethyl)-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl propionamide;

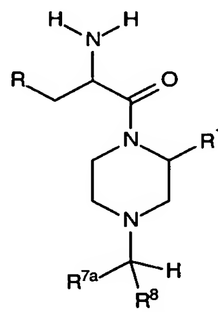
2-{4-[2-Acetylamino-3-(4-fluorophenyl)propionyl]-3-(1-methylethyl)-2-oxo-piperazin-1-yl}-*N*-cyclopropyl-3-naphthalen-2-yl propionamide;

2-{4-[2-Acetylamino-3-(4-chlorophenyl)propionyl]-3-propyl-2-oxo-piperazin-1-yl}-*N*-cyclopropyl-3-naphthalen-2-yl propionamide;

The Category III melanocortin receptor ligands according to the present invention comprises the 2-hydrocarbyl-piperazines having the general scaffold with the formula:



the first aspect of which comprises compounds having the formula:



wherein R is a substituted phenyl unit as described herein above and non-limiting examples of R^1, R^{7a}, and R^8 are defined herein below in Table VIII and in the examples which follow.

TABLE VIII

No.	R^1	R^{7a}	R^8
714	methyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
715	ethyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
716	propyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
717	*iso*-propyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
718	cyclopropyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
719	cyclopropylmethyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
720	allyl	$-C(O)NH_2$	naphthylen-2-ylmethyl
721	methyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
722	ethyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
723	propyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
724	*iso*-propyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
725	cyclopropyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
726	cyclopropylmethyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
727	allyl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl

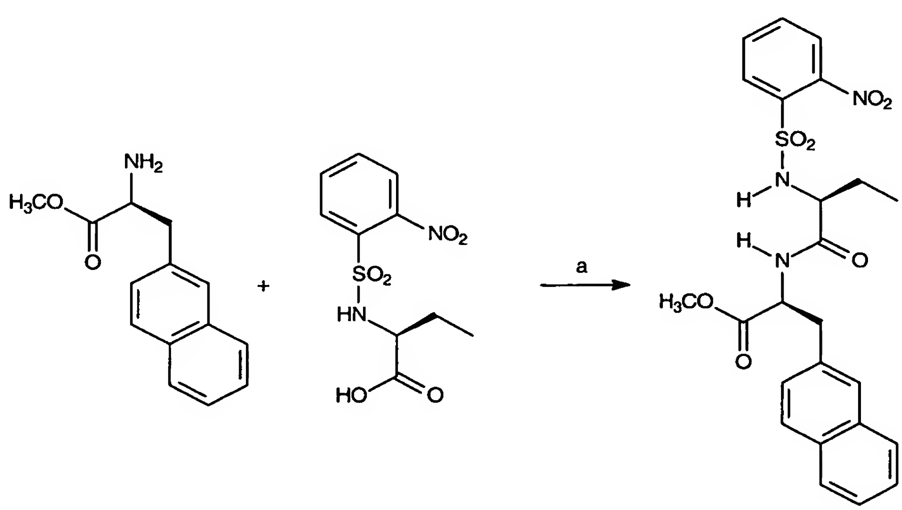
728	methyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
729	ethyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
730	propyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
731	*iso*-propyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
732	cyclopropyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
733	cyclopropylmethyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
734	allyl	$-C(O)NH_2$	(2-chlorophenyl)methyl
735	methyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
736	ethyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
737	propyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
738	*iso*-propyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
739	cyclopropyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
740	cyclopropylmethyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
741	allyl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
742	methyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
743	ethyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
744	propyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
745	*iso*-propyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
746	cyclopropyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
747	cyclopropylmethyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
748	allyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
749	methyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
750	ethyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
751	propyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
752	*iso*-propyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
753	cyclopropyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
754	cyclopropylmethyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
755	allyl	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
756	methyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
757	ethyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
758	propyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
759	*iso*-propyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
760	cyclopropyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
761	cyclopropylmethyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
762	allyl	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
763	methyl	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl

764	ethyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
765	propyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
766	*iso*-propyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
767	cyclopropyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
768	cyclopropylmethyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
769	allyl	-C(O)N(CH_3)$_2$	(3,4-dichlorophenyl)methyl
770	methyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
771	ethyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
772	propyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
773	*iso*-propyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
774	cyclopropyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
775	cyclopropylmethyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
776	allyl	-C(O)N(CH_3)$_2$	(2-chlorophenyl)methyl
777	methyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
778	ethyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
779	propyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
780	*iso*-propyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
781	cyclopropyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
782	cyclopropylmethyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
783	allyl	-C(O)NH(CH_2CH_2F)	naphthylen-2-ylmethyl
784	methyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
785	ethyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
786	propyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
787	*iso*-propyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
788	cyclopropyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
789	cyclopropylmethyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
790	allyl	-C(O)NH(CH_2CH_2F)	(3,4-dichlorophenyl)methyl
791	methyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
792	ethyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
793	propyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
794	*iso*-propyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
795	cyclopropyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
796	cyclopropylmethyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
797	allyl	-C(O)NH(CH_2CH_2F)	(2-chlorophenyl)methyl
798	methyl	-C(O)NHCH_3	(3-chlorophenyl)methyl
799	ethyl	-C(O)NHCH_3	(3-chlorophenyl)methyl

800	propyl	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
801	methyl	$-C(O)N(CH_3)_2$	(3-chlorophenyl)methyl
802	ethyl	$-C(O)N(CH_3)_2$	(3-chlorophenyl)methyl
803	propyl	$-C(O)N(CH_3)_2$	(3-chlorophenyl)methyl
804	methyl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
805	ethyl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
806	propyl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
807	methyl	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
808	ethyl	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
809	propyl	$-C(O)N(CH_3)_2$	(4-chlorophenyl)methyl
810	methyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
811	ethyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
812	propyl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
813	methyl	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
814	ethyl	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
815	propyl	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl

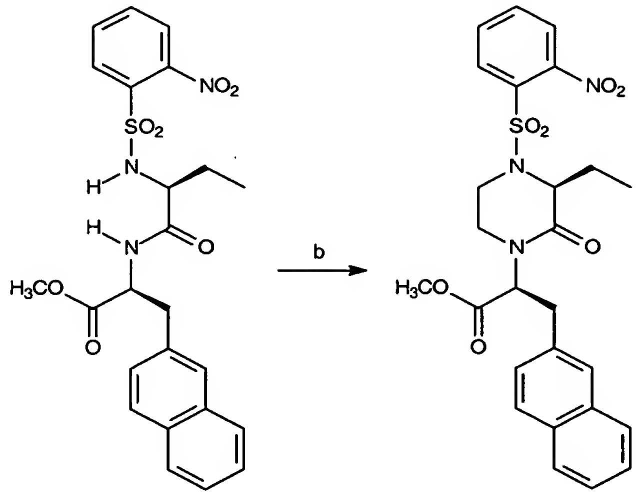
The compounds of the first aspect of Category II can be suitably prepared by the procedure outlined herein below in Scheme X.

Scheme X



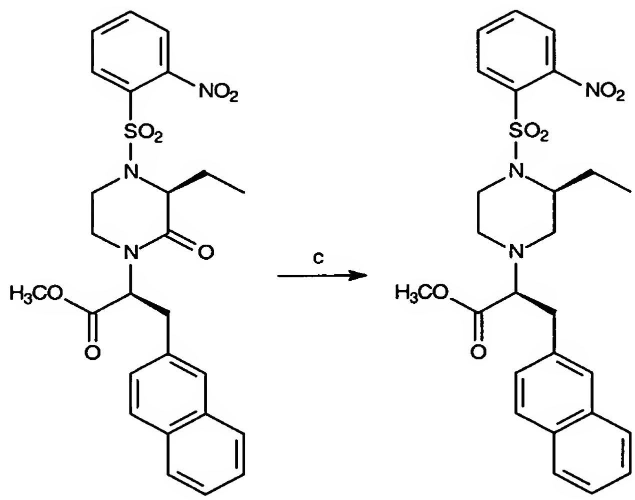
31

Reagents and conditions: (a) EDCI, HOBt, NMM, DMF; 0 °C, 18 hr.



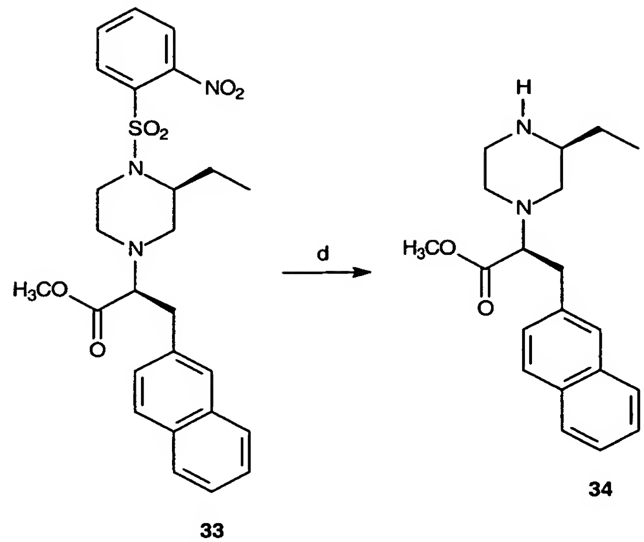
31 32

Reagents and conditions: (b) 1,2-dibromoethane, K_2CO_3, DMF; 60 °C, 17 hr.

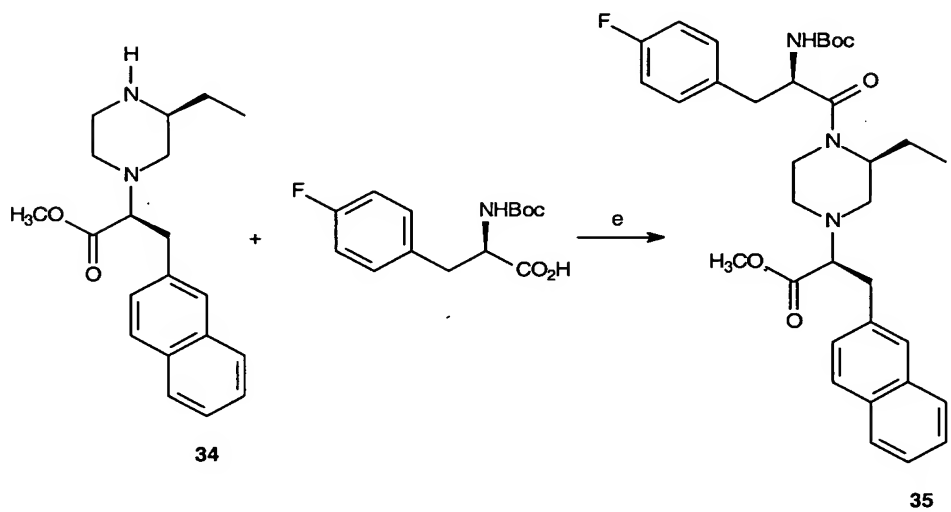


32 33

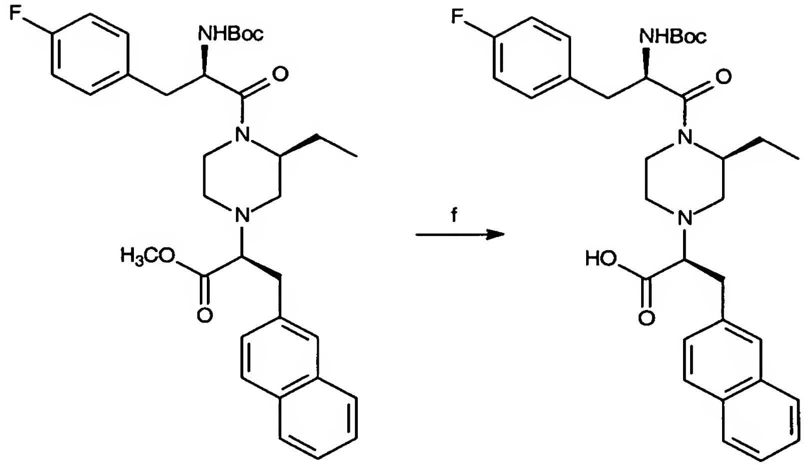
Reagents and conditions: (c) BH_3:THF, CH_2Cl_2; -20 °C, 15 hr.



Reagents and conditions: (d) 4-mercaptophenol, K_2CO_3, DMF; rt, 6 hr.

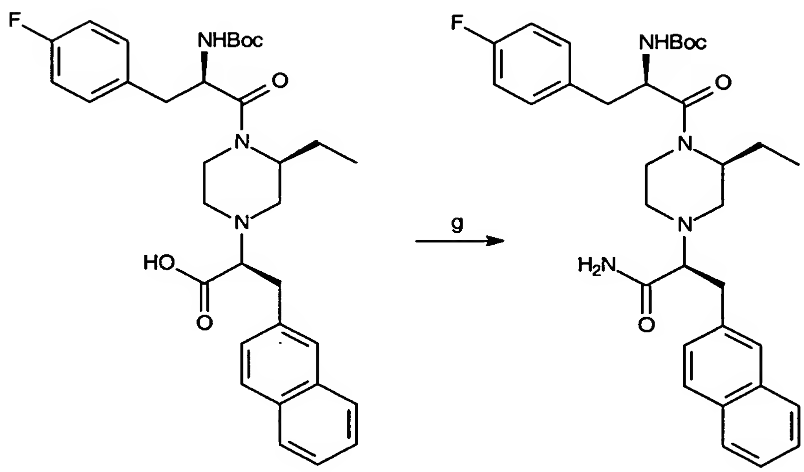


Reagents and conditions: (e) HATU, NMM, DMF; 0 °C, 18 hr.



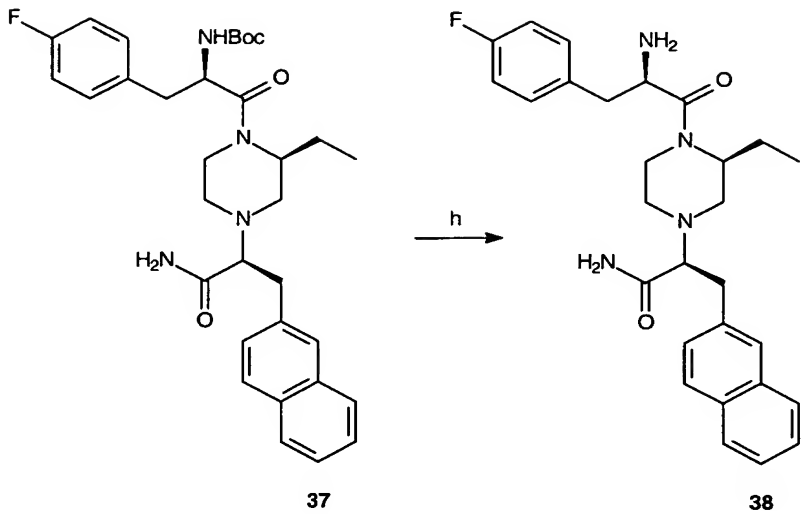
35 36

Reagents and conditions: (f) LiOH, THF/H_2O; rt, 18 hr.



36 37

Reagents and conditions: (g) TOTT, NH_4Cl, DIEA, DMF; rt 1 hr.



Reagents and conditions: (h) HCl, dioxane; rt 1 hr.

EXAMPLE 10

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide HCl (38):

Preparation of 3-naphthalen-2-yl-2-[2-(2-nitro-benzenesulfonylamino)-butyryl-amino]-propionic acid methyl ester (31): 2-Amino-3-naphthen-2-yl-propionic acid methyl ester hydrochloride (1401 g, 53.2 mmol) and 2-(2-nitrobenzenesulfonyl-amino)-butyric acid (19.7 g, 68.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (13.4 g, 106.4 mmol) and 1-hydroxybenzotriazole (12.3 g, 63.9 mmol) are dissolved in anhydrous DMF (75 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (17.5 mL, 160.0 mmol) is added. The reaction mixture is placed in a refrigerator overnight. EtOAc (100 mL) and water (800 mL) are added and the organic layer is decanted. The aqueous layer is extracted with EtOAc (3 x 200 mL), the organic layers combined, washed with water (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 26.6 g, (quantitative yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.90 (d, J = 10.2 Hz, 1H), 7.76 – 7.65 (m, 4H), 7.55 – 7.38 (m, 5H), 7.12 – 7.08 (m, 1H), 6.67 (d, J = 11.7 Hz, 1H), 6.05 (d, J = 11.7 Hz, 1H), 4.72 (quartet, J = 7.3 Hz,1H), 3.88 – 3.79 (m, 1H), 3.60 (s, 3H), 3.20 (double quartet, J = 14.6, 7.3 Hz, 1H), 1.75 – 1.45 (m,2H), .070 (t, J = 11.7 Hz, 3H); ^{13}C NMR, δ 175.0, 171.0, 148.0, 134.0, 133.8, 133.6, 133.2, 132.9, 130.9, 130.3, 128.7, 128.4, 128.0, 127.6, 126.7, 126.3, 125.8, 59.3, 53.8, 52.9, 38.4, 36.9, 31.9, 26.8, 9.8.

Preparation of 2-[3-ethyl-4-(2-nitrobenzenesulfonyl)-2-oxo-piperazin-1yl]-3-naphthalen-2-yl-propionic acid methyl ester (32): To a solution of 3-naphthalen-2-yl-2-[2-(2-nitrobenzenesulfonylamino)-butyryl amino]-propionic acid methyl ester, **31**, (26.6g, 53.2 mmol) in

anhydrous DMF (100 mL) is added 1,2-dibromoethane (100.0g, 532.0 mmol) and potassium carbonate (66.1g, 479.0 mmol). The reaction mixture is heated at 60 °C over night. The reaction mixture is cooled in an ice bath and the pH is adjusted to ~3 with 1M $KHSO_4$. The reaction mixture is extracted with EtOAc (3x300 mL). The organic layers are combined and washed with water (200 mL), dried over Na_2SO_4 and concentrated *in vacuo* and the resulting residue is purified over silica (Hexane: EtOAc 1:1; 5% MeOH in EtOAc) to afford 27.4 g (98% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 8.02- 7.90 (m, 1H), 7.84 – 7.70 (m, 3H), 7.64 – 7.58 (m, 3H), 7.55 – 7.50 (m, 1H), 7.50 – 7.40 (m, 2H), 7.30 (d, J = 6.0 Hz, 1H), 5.35 (dd, J – 12.0, 4.8 Hz, 1H), 4.25 (t, J = 7.2 Hz, 1H, 3.78 – 3.68 (m, 1H), 3.65 (s, 3H), 3.52 (dd, J = 15.0, 6.0 Hz, 1H), 3.30 – 3.10 (m, 4H), 1.58 – 1.50 (m, 1H), 1.42 – 1.38 (m, 1H), 0.56 (t, J = 7.2 Hz, 3H); ^{13}C NMR, δ 170.5, 167.8, 148.0, 134.2, 134.0, 133.6, 133.1, 132.6, 132.3, 130.9, 128.5, 127.9, 127.7, 127.5, 126.9, 126.5, 126.0, 124.6.

Preparation of 2-[3-ethyl-4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-3-naphthalen-2-yl-prppionic acid methyl ester (33): To a solution of 2-[3-ethyl-4-(2-nitrobenzenesulfonyl)-2-oxo-piperazin-1yl]-3-naphthalen-2-yl-propionic acid methyl ester, **32**, (5.3g, 10. mmol) in anhydrous THF (10 mL) is added 1.0 M borane-tetrahydrofuran complex (32.0 mL) at –20 °C. The reaction mixture is stirred at this temperature overnight. Methanol (3 mL) is added to the reaction mixture at –20 °C and the solution is allowed to stir for twenty minutes. Additional methanol (6 mL) is added and the reaction mixture is allowed to warm to room temperature. The solvent is removed *in vacuo* and the product is purified over silica (EtOAc/Hexane: 1:1) to afford 4.1g (68% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 8.04 – 7.98m, (1H), 7.80 – 7.72 (m, 3H), 7.61 – 7.52 (m, 4H), 7.45 – 7.38 (m, 2H), 7.28 (d, J = 9.6 Hz, 1H), 3.78 (t, J = 6.0 Hz, 1H), 3.64 (d, J = 11.0 Hz, 1H), 3.50 (s, 3H), 3.48 (t, J = 7.2 Hz, 1H), 3.24 – 3.10 (m, 2H), 3.10 – 2.95 (m, 1H), 2.90 (t, J = 11.0 Hz, 1H), 2.66 (d, J = 2.4 Hz), 2.38 – 2.20 (m, 1H), 1.61 – 1.48 (m, 1H), 1.48 – 1.32 (m, 1H), 0.58 (t, J = 9.6 Hz, 3H);); ^{13}C NMR, δ 171.7, 148.0, 135.9, 134.2, 133.7, 132.4, 132.0, 130.9, 128.0, 127.7, 127.6, 126.2, 125.6, 124.4, 69.0, 56.4, 53.8, 51.3, 47.0, 41.9, 35.2, 22.2, 10.7.

Preparation of 2-(3-ethyl-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester (34): To a solution of 2-[3-ethyl-4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-3-naphthalen-2-yl-prppionic acid methyl ester, **33**, (4.1g, 8.0 mmol) in anhydrous DMF (40 mL) is added potassium carbonate (6.7g, 48.2 mmol) and 4-mercaptophenol (3.0 g, 24.1 mmol). The reaction mixture is stirred for six hours at room temperature, cooled in a ice bath and the pH adjusted to ~3 with 1M HCl. The reaction mixture is extracted with Et_2O (4 x 100 mL), the organic layers combined and extracted with 1M HCl (100 mL). The organic layers are then discarded. The aqueous layers were combined and cooled in ice bath and pH was adjusted to ~10 with K_2CO_3.

The aqueous layer is extracted with EtOAc (4 x 125 mL) and dried over Na_2SO_4. The combined organic layers are concentrated *in vacuo* to afford 2.1 g (80% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.84 – 7.75 (m, 3H), 7.70 (s, 1H), 7.50 – 7.38 (m, 2H), 7.35 (dd, J = 8.3, 1.7 Hz, 1H), 3.60(s, 3H), 3.55 – 3.50 (m, 1H), 3.30 – 3.24 (m, 1H), 3.18 – 3.08 (m, 1H), 3.05 –2.75 (m, 5H), 2.70 – 2.55 (m, 1H), 2.50 (dd, J = 10.4, 4.1 Hz, 1H), 2.04 (t, J = 10.4 Hz, 1H), 1.52 – 1.32 (M, 2H), 1.00 (t, J = 8.3 Hz, 3H); ^{13}C NMR, δ 171.8, 135.9, 133.7, 132.4, 128.1, 128.0, 127.9, 127.8, 126.1, 125.6, 120.8, 70.0, 57.3, 54.3, 52.9, 51.3, 46.4, 35.7, 27.5, 10.6.

Preparation of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (35): 2-(3-Ethyl-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester, **34**, (2.1 g, 6.4 mmol) and *N*-Boc-D-4-fluorophenylalanine (1.9 g, 6.8 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (4.9 g, 12.9 mmol) are dissolved in anhydrous DMF (20 mL). This reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.75 mL, 6.8 mmol) is added. The reaction mixture is placed in a refrigerator overnight. EtOAc (75 mL) and water (300 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x150 mL). The combined organic layers are washed with water (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue is purified over silica (EtOAc/Hexane, 1:2) to afford 3.5 g (91% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.82 – 7.75 (m, 3H), 7.62 (s, 1H), 7.52 – 7.40 (M, 2H), 7.34 (m, 1H), 7.22 – 7.25 (m, 2H), 7.02 – 6.92 (m2H), 5.75 – 5.62 (M, 1H), 5.18 (d, J = 7.7Hz, 0.5H), 4.90 (quartet, J = 7.7 Hz, 1H), 4750 – 4.62 (m, 0.5 H), 4.50 – 4.25 (m, 1H), 3.64 (d, J = 9.7 Hz, 3H),3.58 –3.38 (m, 1.5H), 3.30 – 2.90 (m, 6H), 2.90 – 2.70 (m, 1H), 2.62 - 2.25 (d, J = 11.6 Hz,1H), 2.15 – 2.00 (m, 1H), 1.78 – 1.50 (m, 1.5H), 1.42 (s, 9H), 1.35 – 1.20 (m, 1H), 0.6 (t, J = 9.7 Hz, 2H); ^{13}C NMR, δ 174.2, 171.6, 171.0, 170.2, 164.0, 160.2, 156, 135.7, 133.7, 132.4, 131.4, 131.3, 128.1, 127.8, 127.6, 127.5, 126.2, 125.7, 115.7, 115.5, 115.4, 115.3, 79.9, 68.9, 68.7, 55.9, 54.1, 53.7, 51.4, 51.2, 51.0, 47.5, 46.6, 40.1, 39.1, 38.1, 35.4, 28.5, 22.9, 21.9, 10.6, 10.0

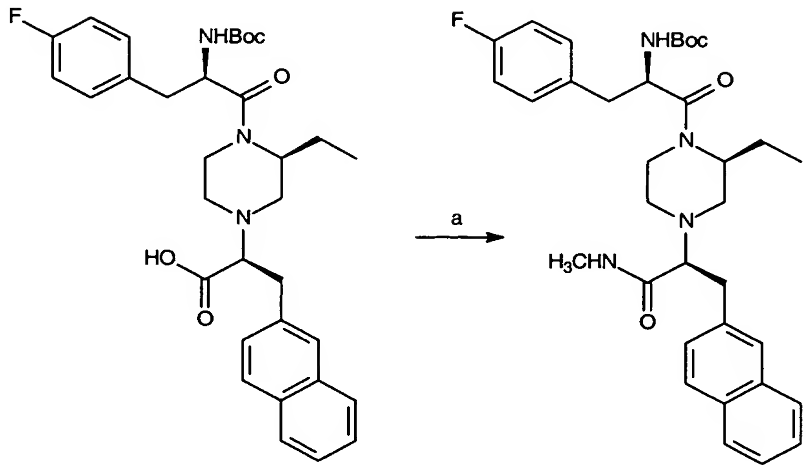
Preparation of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (36): LiOH (0.61 g, 25.5 mmol) is added to a cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **35**, (3.5 g, 5.9 mmol) in THF/H_2O (2:1, 36 mL). The reaction mixture is stirred overnight. The reaction mixture is cooled in a ice bath and the pH is adjusted to 3 with 1M HCl. The aqueous layer is extracted with EtOAc (3 x 100 mL) and dried over Na_2SO_4. The organic layers are combined and concentrated *in vacuo* to afford 3.4 g (98% yield) of the desired product.

Preparation of [2-[4-(1-carbamoyl-2-naphthalen-2-yl-ethyl)-2-ethyl-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (37): To solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid, **36**, (0.3g, 0.5 mmol) and 2-(1-oxy-pyridine-2-yl)-1,1,3,3-tetramethylisothiouronium tetrafluoroborate (TOTT) (0.24 g, 0.8 mmol) in DMF (2.0 mL) are added ammonium chloride (0.06 g, 1.0mmol) and DIEA (0.2 mL, 1.0 mmol). The reaction mixture is stirred at room temperature for 1hour then a saturated solution of ammonium chloride (30 mL) is added. The reaction mixture is extracted with EtOAc (3 x 30 mL), then the combined organic layers are washed with 2M HCl (2 x 10 mL), water (2 x 10 mL), a saturated solution of sodium bicarbonate (2 x 10 mL), water (2 x 10 mL) and dried over Na_2SO_4. The solution is concentrated *in vacuo* to afford 0.26 g (87% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.75 – 7.55 (m, 4H), 7.38 – 7.20 (m ,3H), 7.10 – 7.00 (m, 2H), 6.90 – 6.80 (m, 2H), 6.40 – 6.00 (m, 1H), 5.55 – 5.25 (m, 1H), 4.45 – 4.18 (m, 1H), 3.60 – 2.00 (m, 10H), 1.80 – 1.32 (m, 2H), 1.32 – 1.18 (m, 11H), 0.70 – 0.55 (m, 3H); ^{13}C NMR, δ 175.0, 172.0, 171.0, 170.0, 164.0, 160.0, 155.2, 137.3, 133.8, 132.6, 132.4, 131.5, 131.4, 131.3, 131.2, 131.1, 128.4, 128.0, 127.8, 126.4, 125.8, 116.0, 115.8, 115.7, 115.6, 115.4, 80.4, 80.0, 70.6, 70.3, 60.7, 55.5, 51.8, 51.4, 51.1, 50.8, 50.4, 41.9, 40.2, 39.2, 38.0, 37.9, 32.6, 28.6, 23.3, 22.4, 21.4, 14.5, 10.9, 10.3.

Preparation of 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide HCl (38): [2-[4-(1-carbamoyl-2-naphthalen-2-yl-ethyl)-2-ethyl-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester, **37**, (0.26g, 0.5 mmol) is dissolved in 4M HCl in dioxane (7 mL). The reaction mixture is stirred for 60 minutes, then 1,2-dichloroethane (7 mL) is added. The solution is concentrated *in vacuo* to afford 0.24 g (quantitative yield) of the desired product.

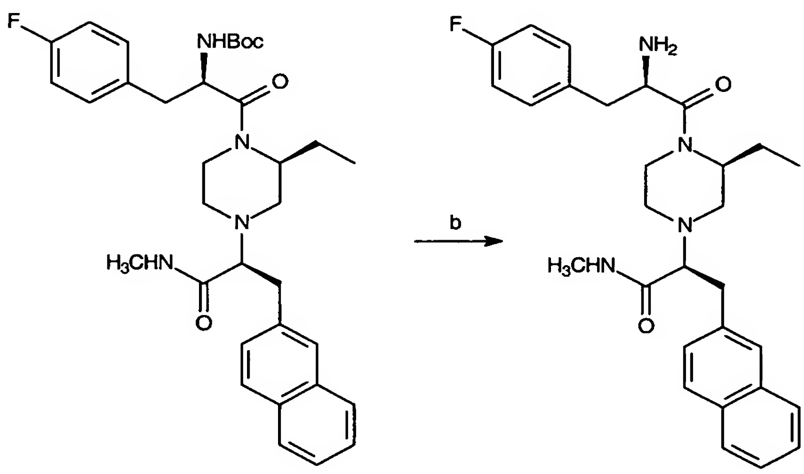
Other iterations of R^{7a} can be obtained from Intermediate **36** as outlined in Scheme XI.

Scheme XI



36 40

Reagents and conditions: (a) CH_3NH_2, PyBOP, TEA, CH_2Cl_2; rt, 18 hr



40 41

Reagents and conditions: (b) HCl, CH_2Cl_2; rt, 1 hr.

EXAMPLE 11

2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide Hydrochloride (41)

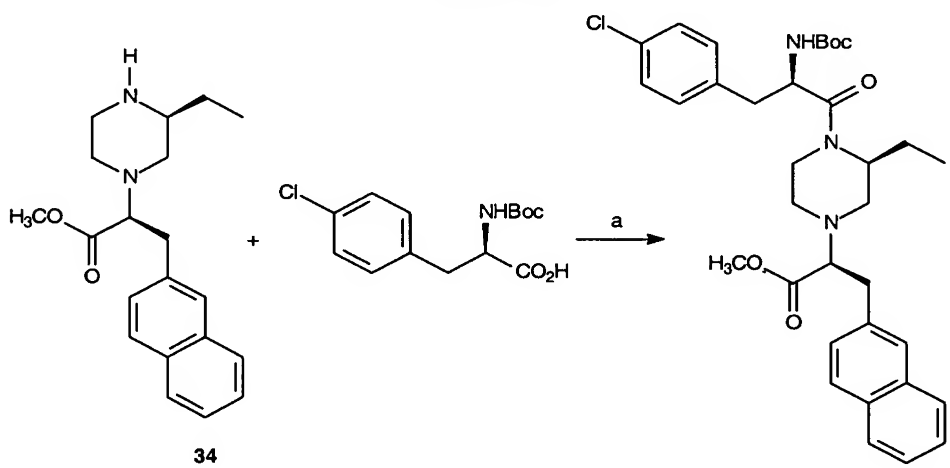
Preparation of [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (40): To a cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid, **36**, (1.7g, 3.0 mmol) and benzotriazole-1-yl-oxy-tris-pyrrolidinol-phosphonium hexafluorophosphate (PyBOP) (2.0 g, 3.8 mmol) in anhydrous dichloromethane (10 mL) are added 2 M methyl amine solution in THF (1.5 mL, 3.0 mmol) and triethyl amine (1.0 mL,

7.4 mmol). The reaction mixture is placed in a refrigerator overnight. EtOAc (50 mL) and water (200 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x100 mL). The combined organic layers are washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product is purified over silica (EtOAc/hexane, 1:1) to afford 1.3 g (73% yield) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.75 – 7.65 (m, 3H), 7.55 (s, 1H), 7.39 – 7.29 (m, 2H), 7.29 – 7.2 (m, 1H), 7.10 – 7.02 (m, 2H), 6.90 – 6.82 (m, 2H), 6.51 – 6.30 (m, 1H), 5.31 (d, J = 10.4 Hz, 1H), 4.85 – 4.15 (m, 2.5H), 3.55 – 3.12 (m, 3H), 3.00 – 2.05 (m, 10H), 1.85 – 1.45 (m, 10H), 0.7 (m, 3H); ^{13}C NMR, ($CDCl_3$, 300 MHz) δ 174.0, 172.0, 171.0, 170.0, 163.9, 160.6, 155.2, 137.4, 133.8, 132.4, 131.5, 131.4, 131.3, 131.2, 128.4, 128.0, 127.8, 126.4, 125.8, 116.0, 115.7, 115.4, 80.0, 70.9, 70.7, 60.7, 55.4, 52.1, 51.2, 51.0, 50.5, 49.8, 41.9, 40.2, 39.4, 38.0, 32.4, 28.6, 26.3, 23.3, 22.3, 21.4, 14.5, 10.8, 10.3.

Preparation of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide Hydrochloride (41): [2-[2-Ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester, **40**, is dissolved in 4M HCl in dioxane (20 mL). The reaction mixture is stirred for 1 hour, then 1,2-dichloroethane (20 mL) is added. Solvent is removed *in vacuo* to afford 1.1 g (99% yield) of the desired product.

Scheme XII illustrates the replacement of 4-fluorophenyl as the R unit with 4-chlorophenyl.

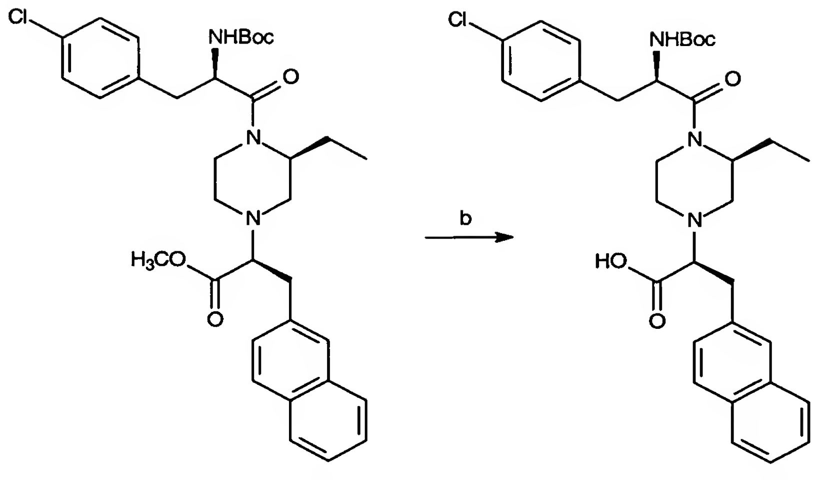
Scheme XII



34

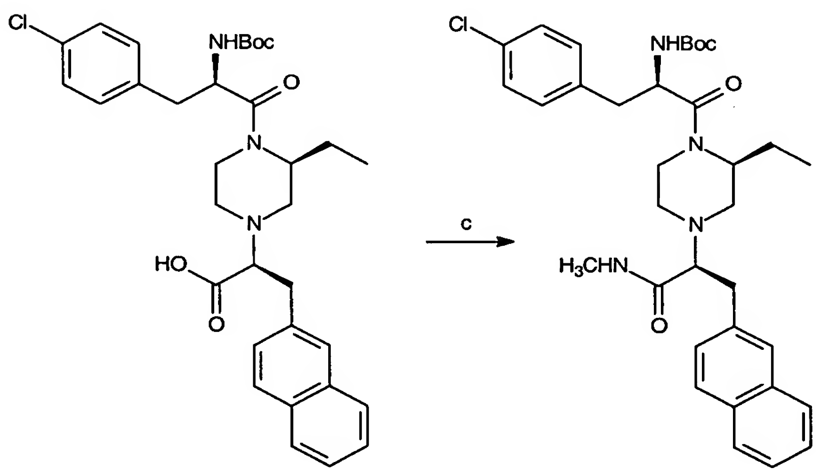
42

Reagents and conditions: (a) HATU, NMM, DMF; 0 °C, 18 hr.



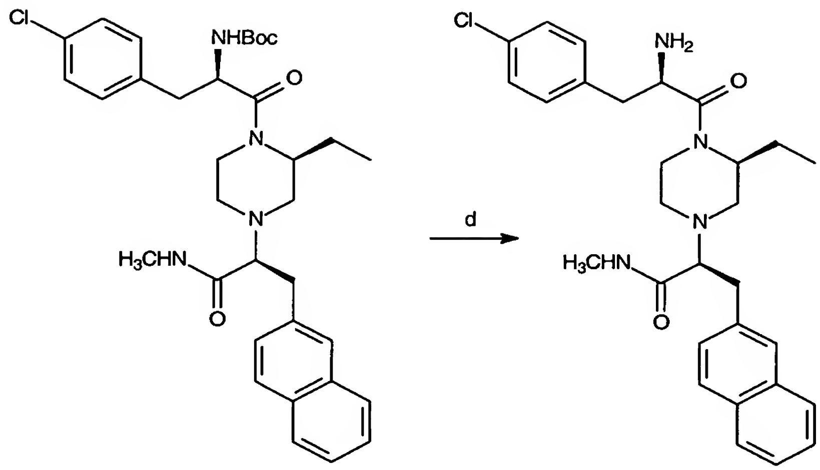
42 43

Reagents and conditions: (b) LiOH, THF/H_2O; rt, 18 hr.



43 44

Reagents and conditions: (c) CH_2NH_2, PyBOP, TEA, THF; 0 °C, 18 hr.



44 **45**

Reagents and conditions: (d) 4 N HCl, dioxane; rt, 1 hr.

EXAMPLE 12

2-{4-[2-amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide HCl (45)

Preparation of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (42): 2-(3-Ethyl-piperazin-1-yl)-3-naphthalen-2-yl-propionic acid methyl ester, **34**, (0.52 g, 1.6 mmol) and Boc-D-4-chlorophenylalanine (0.5 g, 1.7 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium hexafluoro-phosphate (1.2 g, 3.2 mmol) are dissolved in anhydrous DMF (20 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.35 mL, 3.2 mmol) is added. The reaction mixture is placed in a refrigerator overnight. EtOAc (75 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x50 mL). All organic layers are combined and washed with water (20 mL), and dried over Na_2SO_4. The organic layers are concentrated *in vacuo* to afford 1.0 g (quantitative yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.70 – 7.65 (m, 3H), 7.52 (s, 1H), 7.35 – 7.32 (m, 2H), 7.22 – 7.13 (m, 4H), 7.07 – 7.02 (m, 2H), 5.59 (dd, J = 13.5, 8.7 Hz, 1H), 4.74 (q, J = 7.5 Hz, 1H), 2.28 – 4.21 (m, 1H), 3.53 (d, J = 12.3 Hz, 3H), 3.42 – 3.08 (m, 2H), 3.04 – 2.81 m, 4H), 2.80 (s, 1H), 2.75 (s, 3H), 2.64 – 2.60 (m, 1H), 2.46 (t, J = 10.5 Hz, 1H), 2.20 – 2.05 (m, 1H), 1.55 – 1.40 (m, 1H), 1.18 (s,9H), 0.54 – 0.47 (m, 2H); ^{13}C NMR, δ 171.6, 170.5, 170.0, 162.9, 155.0, 150.7, 135.8, 135.2, 133.6, 132.8, 132.4, 131.1, 131.2, 128.9, 128.7, 128.6, 128.0, 127.7, 127.6, 126.2, 125.6, 124.5, 120.4, 79.7, 68.9, 60.5, 55.8, 53.7, 51.4, 51.0, 47.4, 47.0, 41.5, 40.0, 39.0, 38.7, 38.0, 36.6, 35.3, 35.0, 31.6, 28.4, 22.8, 21.8, 21.1, 14.3, 10.5, 10.0.

Preparation of 2-{4-[2-tert-butoxycarbonylamino-3-(4-chlorophenyl)-propionyl}-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid (43): LiOH (0.2g, 7.9 mmol) is added to the cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **42**, (1.0 g, 1.6 mmol) in THF/H_2O (2/1, 30mL). The reaction mixture is stirred overnight. The reaction mixture is cooled in ice bath and the pH is adjusted to 3 with 1M HCl. The aqueous layer is extracted with EtOAc (3 x 75 mL) and dried over Na_2SO_4. The organic layers are concentrated *in vacuo* to afford 1.0 g (quantitative yield) of the desired product.

Preparation of {1-(4-chlorobenzyl)-2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (44): To a cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid, **43**, (1.0g, 1.6 mmol) and PyBOP (1.1 g, 2.0 mmol) in anhydrous dichloromethane (10 mL) are added 2 M methyl amine solution in THF (0.9 mL, 1.6 mmol) and triethyl amine (0.6 mL, 3.9 mmol). The reaction mixture is placed in a refrigerator overnight. EtOAc (50 mL) and water (100 mL) are added, the organic layer is decanted and the aqueous layer is extracted with EtOAc (3 x 75 mL). All organic layers are combined and washed with brine (100 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified over silica (EtOAc/Hexane, 1:1) to provide 1.0 g (quantitative yield) of the desired product. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 – 7.50 (m, 4H), 7.29 – 7.14 (m, 4H), 7.10 – 7.04 (m, 2H), 7.00 – 6.97 (m, 3H), 5.60 – 5.51 (m, 1H), 4.73 – 4.66 (m, 1H), 4.30-4.11 (m, 1H), 3.45 – 3.26 (m, 2H), 3.15 – 3.05 (m, 1H), 2.86 - 2.79 (m, 3H), 2.75 –2.59 (m, 5H), 2.56 – 2.47 (m, 1H), 2.43 – 2.29 (m, 1H), 2.05 – 2.01 (m,1H), 1.61 (s, 9H), 0.64 – 0.54 (m, 2); ^{13}C NMR, ($CDCl_3$, 75 MHz): δ. 171.9, 170.3, 170.0, 155.0, 137.4, 137.2, 135.3, 135.1, 133.6, 132.8, 132.2, 131.2, 131.1, 131.0, 128.7, 128.6, 128.4, 127.9, 127.8, 127.6, 127.5, 126.4, 126.0, 125.4, 124.7, 118.6, 110.4, 79.6, 69.9, 55.4, 50.9, 50.2, 46.4, 39.8, 37.9, 32.0, 32.6, 28.4, 26.5, 26.1, 23.0, 22.0, 10.6, 10.0.

Preparation of 2-{4-[2-amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide HCl (45): {1-(4-Chlorobenzyl)-2-[2-ethyl-4-(1-methylcarbamo yl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl]-carbamic acid *tert*-butyl ester, **44**, (1.0 g, 1.6 mmol) is dissolved in 4M HCl in dioxane (20 mL). The reaction mixture is stirred for 60 minutes then 1,2-dichloroethane (20 mL) is added. Solvent is removed *in vacuo* to afford 1 g (quantitative yield) of the desired product.

The following are non-limiting examples of analogs which comprise the first aspect of Category III according to the present invention.

2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (300 MHz, ppm ,CD_3OD), rotamers: δ 7.78-7.76, m, 3H; 7.65, s, 1H; 7.43-7.31, m, 5H; 7.11-7.15, m, 2H; 4.72-4.67, m, 0.5H, 4.54-4.49, m, 1H; 4.34-4.29, m, 0.5H; 3.64-3.54, m, 1H; 3.42-3.31, m, 3H; 3.26-2.98, m, 7H; 2.88-2.81, m, 1H; 2.71-2.58, m, 5H; 1.58-1.23, m, 2H; 1.08, m, 2H; 0.78-0.72, m, 3H. Carbon ^{13}NMR (300 MHz, ppm ,CD_3OD), rotamers: δ 171.10, 170.57, 166.91, 164.36, 161.12, 135.57, 135.05, 133.79, 132.66, 131.78, 131.66, 131.54, 131.44, 130.00, 127.82,127.74, 127.42, 127.29, 125.95, 125.89, 125.48, 125.37, 116.01, 115.80, 115.51, 54.31, 52.91, 52.08, 50.90, 50.60, 49.84, 40.98, 37.92, 37.11, 36.31, 34.33, 34.29, 31.86, 30.99, 24.70, 19.17, 18.99, 12.80, 12.86. MS(ESI) m/e 505 [M+1].

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz): δ with rotamers 7.34-7.08 (m, 8H), 4.72-4.37 (m, 2H), 3.68-3.41 (m, 2H), 3.23-2.84 (m, 8H), 2.67, 2.62 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.40-1.68 (m, 1H), 1.49 (m, 2H), 1.17 (m, 2H), 0.90 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.0, 172.0, 169.0, 166.0, 162.8, 162.7, 162.3, 138.3, 137.6, 134.1, 133.8, 133.4, 133.3, 133.2, 133.1, 132.3, 131.6, 129.9, 129.8, 117.6, 117.4, 117.3, 117.1, 112.3, 71.1, 70.9, 55.8,54.3, 53.6, 52.5, 52.2, 51.2, 50.3, 38.7, 37.9, 34.9, 33.5, 32.6, 26.3, 20.8, 20.6, 14.6, 14.5; MS *m/z* (ESI): 489 (M + H, 100), 491 (M + 2 + H, 37).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2-chlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.21-6.94 (m, 8H), 4.53-4.13 (m, 2H), 3.39-3.26 (m, 1H), 3.04-2.57 (m, 7H), 2.51, 2.49 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.36 (m, 2H), 1.98-1.47 (m, 1H), 1.31-1.11 (m, 2H), 0.95 (m, 2H), 0.67 (t, 3H, J = 7.1 Hz); ^{13}C NMR (CD_3OD, 5 MHz with rotamers) δ 173.2, 173.0, 168.3, 166.0,162.7, 137.8, 137.6, 135.6, 133.4, 133.3, 133.2, 133.1, 131.6, 130.9, 129.7, 129.6, 128.3, 117.6, 117.4, 117.3, 117.1, 114.1, 69.4, 69.2, 56.2, 54.6, 53.6, 52.5, 52.1, 51.9, 43.2, 39.9, 38.8, 38.0, 33.5, 32.5, 26.2, 20.8, 20.6, 14.7; MS *m/z* (ESI): 489 (M + H, 100), 491 (M + 2 + H, 37).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3-chlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.22-6.96 (m, 8H), 4.93-4.21 (m, 2H), 3.50-3.13 (m, 2H), 2.97-2.79 (m, 6H), 2.57, 2.53 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.45 (m, 2H), 2.12-1.55 (m, 1H), 1.37(m, 2H), 1.03 (m, 2H), 0.79 (t, 3H, J = 7.1 Hz); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 172.7, 172.4, 168.5, 166.0, 162.7, 142.5, 142.0, 135.5, 135.4, 133.4, 133.3, 133.1, 133.0, 131.6, 131.2, 130.8, 129.1, 128.1, 127.9, 117.6, 117.4, 117.3, 117.1, 71.0, 70.8, 56.0, 54.6, 53.7, 52.5, 52.2, 51.7, 42.9, 39.7, 38.7, 37.9, 35.4, 35.2, 33.5, 32.6, 26.2, 20.8, 20.6, 14.7, 14.6; MS *m/z* (ESI): 489 (M + H, 100), 491 (M + 2 + H, 37).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2,4-dichlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.44 (m, 1H), 7.33-7.14 (m, 4H), 7.12 (m, 2H), 4.69-4.25 (m, 2H), 3.56-3.40 (m, 1H), 3.29-2.78 (m, 7H), 2.70, 2.67 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.55-2.38 (m, 2H), 2.12-1.60 (m, 1H), 1.42-1.25 (m, 2H), 1.10 (m, 2H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.0, 172.9, 168.5, 166.0, 162.7, 136.9, 136.6, 136.4, 134.5, 134.4, 133.4, 133.3, 133.2, 133.1, 131.6, 130.5, 128.5, 117.6, 117.4, 117.3, 117.2, 69.2, 68.9, 56.2, 54.7, 53.8, 52.5, 52.1, 51.9, 43.1, 39.8, 38.8, 38.0, 33.5, 32.9, 32.8, 32.6, 26.2, 20.8, 20.6, 14.7, 14.6; MS *m/z* (ESI): 523 (M + H, 100), 525 (M + 2 + H, 70).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-(2-fluoroethyl)-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.40-7.17 (m, 8H), 4.76-4.29 (m, 4H), 3.69-3.37 (m, 4H), 3.25-2.88 (m, 4H), 2.75-2.34 (m, 2H), 1.92 (m, 2H), 1.63-1.18 (m, 3H), 1.24 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 172.6, 172.0, 168.5, 166.0, 162.7, 162.4, 138.6, 138.2, 133.9, 133.7, 133.3, 133.1, 132.3, 131.6, 129.8, 117.6, 117.4, 117.1, 84.5, 82.3, 71.0, 70.9, 55.9, 54.6, 53.6, 52.5, 51.6, 47.8, 42.8, 41.3, 41.0, 39.6, 38.6, 37.9, 35.1, 34.7, 33.6, 32.7, 27.8, 27.7, 20.8, 20.7, 14.7, 14.6; MS *m/z* (ESI): 521 (M + H, 60), 523 (M + 2 + H, 20), 258 (100).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2-fluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.865 (t, 3H, J=6.9Hz), 1.128 (m, 2H), 1.411 (m, 2H), 2.681, 2.719 (2 singlets, 3H, $C\underline{H}_3NHC(O)$, rotamers), 2.856 (m, 3H), 3.072 (m, 5H), 3.338 (m, 3H), 3.529 (d, 1H, J=12.9), 4.465 (d, 1H, J=12.9), 4.515 (m, 2H), 4.705 (t, 1H, J=7.2), 7.103 (m, 4H), 7.300 (m, 4H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 42.462, 46.229, 46.726; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.9, 164.8, 162.7, 161.4, 133.3, 133.1, 133.0, 129.8, 125.5, 117.5, 117.3, 117.2, 117.0, 116.5, 116.2, 69.9, 69.6, 56.2, 54.6, 53.7, 52.4, 52.1, 52.0, 43.3, 40.0, 38.7, 33.4, 32.5, 29.2, 29.0, 26.3, 26.2, 20.7, 20.6, 14.7, 14.6; MS *m/e* 473 (M+1).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3-fluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.921 (t, 3H), 1.200 (m, 2H), 1.511 (m, 2H), 2.643, 2.687 (2 singlets, 3H, $C\underline{H}_3NHC(O)$, rotamers), 2.948 (m, 3H), 3.056 (m, 5H), 3.334 (m, 3H), 3.650 (d, 1H), 4.349 (d, 1H), 4.518 (m, 2H), 4.732 (t, 1H), 6.993 (m, 3H), 7.140 (m, 1H), □ 7.325 (m, 4H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 42.462, 46.229, 46.726; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 166.2, 165.9, 162.7, 142.9, 133.3, 133.2, 133.1, 133.0, 131.6, 131.4, 131.3, 126.5, 117.6, 117.4, 117.3, 117.1, 117.0, 114.7, 114.6, 114.4,

114.3, 71.1, 70.9, 56.0, 54.5, 53.6, 52.5, 52.1, 51.8, 43.1, 39.8, 37.9, 35.5, 33.5, 32.6, 26.2, 20.8, 20.6, 14.6, 14.5; MS *m/e* 473 (M+1).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-fluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.91 (t, 3H, J=6.9), 1.16 (m, 2H), 1.48 (m, 2H), 2.63, 2.67 (2 singlets, 3H, $C\underline{H}_3NHC(O)$, rotamers), 2.88 (m, 3H), 3.08 (m, 5H), 3.36 (m, 3H), 3.60 (d, 1H), 4.31 (d, 1H, J=12.9), 4.54 (m, 2H), 4.711 (t, 1H), 7.01 (m, 2H), 7.15 (m, 4H), 7.32 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 46.718, 47.167, 47.378; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 166.2, 165.9, 162.7, 142.9, 133.3, 133.2, 133.1, 133.0, 131.6, 131.4, 131.3, 126.5, 117.6, 117.5, 117.4, 117.2, 117.1, 114.7, 114.6, 114.4, 114.3, 71.1, 70.9, 56.1, 54.5, 53.6, 52.5, 52.2, 51.8, 50.3, 43.0, 39.9, 37.9, 35.5, 33.5, 32.7, 26.2, 20.8, 20.6, 14.7, 14.6; MS *m/e* 473 (M+1).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-difluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.918 (t, 3H, J=7.2), 1.154 (m, 2H), 1.439 (m, 2H), 2.66, 2.70 (2 singlets, 3H, $C\underline{H}_3NHC(O)$, rotamers), 2.871 (m, 3H), 3.160 (m, 5H), 3.34 (m, 3H), 3.590 (d, 1H, J=13.2), 4.30 (d, 1H, J=13.8), 4.52 (m, 2H), 4.713 (t, 1H), 7.00 (m, 1H), 7.155 (m, 4H), 7.32 (m, 2H); ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.9, 162.7, 150.1, 137.9, 137.6, 133.3, 133.2, 133.1, 133.0, 131.6, 127.1, 119.5, 119.3, 118.4, 118.2, 117.6, 117.3, 117.2, 117.1, 71.1, 70.9, 56.1, 54.6, 53.7, 52.5, 52.2, 51.8, 50.2, 43.2, 38.8, 37.9, 34.9, 33.6, 32.7, 26.2, 20.8, 20.6, 14.7, 14.6; MS *m/e* 491 (M+1).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methyl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.37-7.46 (m, 2H), 7.28-7.37 (m, 2H), 7.07-7.18(m, 3H), 4.73 (t, J = 7.4 Hz, 1H), 4.50-4.61 (m, 1.5H), 4.26-4.38 (m, 0.5H), 3.58-3.68 (m, 0.5H), 3.38-3.47 (m, 0.5H), 3.14-3.28 (m, 1H), 2.78-3.14 (m,6H), 2.71 (s, 1.33H), 2.66 (s, 1.66H), 2.50-2.65 (m, 2H), 1.26-1.72 (m, 2H), 1.01-1.26 (m, 2H), 0.85-0.94 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 170.79, 170.35, 167.04, 166.95, 164.40, 161.14, 161.04, 131.89, 131.28, 131.72, 131.59, 131.49, 131.32, 130.28, 130.19, 130.14, 129.14, 116.02, 115.81, 115.72, 115.53, 69.30, 69.02, 54.46, 53.04, 52.25, 50.89, 50.57, 50.01, 41.14, 38.07, 37.20, 36.39, 33.13, 33.06, 31.94, 31.08, 24.73, 19.25, 19.06, 13.11, 13.04; MS (ESMS) *m/z* 523.4, 525.4, 527.6 $(M+H)^+$, Cl_2 isotope pattern. .

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-(2-fluoroethyl)-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.38-7.47 (m, 2H), 7.28-7.38 (m, 2H), 7.06-7.19 (m, 3H), 4.73 (t, J = 7.5 Hz, 1H), 4.19-4.62 (m, 4H), 3.36-3.70 (m, 3H), 2.75-3.24 (m, 7H), 2.56-2.71 (m, 2H), 1.28-1.76 (m, 2H), 1.03-1.26 (m,

2H), 0.91 (t, J = 7.1Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD, Rotamers) δ 170.49, 169.86, 167.06, 166.98, 164.38, 161.13, 160.82, 160.32, 139.16, 138.68, 131.92, 131.78, 131.67, 131.60, 131.48, 131.34, 130.38, 130.23, 130.04, 129.17, 116.02, 115.82, 115.74, 115.53, 82.90, 80.67, 69.14, 68.95, 54.35, 53.06, 52.18, 50.91, 50.69, 49.98, 41.09, 39.76, 39.48, 37.98, 37.08, 36.38, 33.10, 32.89, 32.00, 31.14, 19.27, 19.09, 13.11, 13.03; MS (ESMS) *m/z* 555.4, 557.4, 559.6 $(M+H)^+$, Cl_2 isotope pattern. .

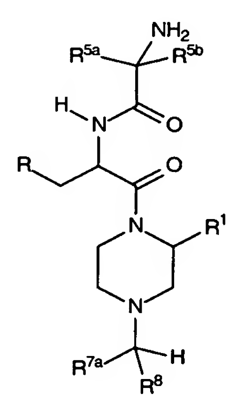
2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-isopropyl-propionamide: ^1H NMR (300 MHz, MeOD, Rotamers) δ 7.29-7.48 (m, 4H), 7.08-7.20 (m, 3H), 4.67-4.76 (m, 0.6H), 4.49-4.59 (m, 1H), 4.26-4.37 (m, 0.4H), 3.83-3.98 (m, 1H), 3.56-3.67 (m, 0.6H), 3.40-3.49 (m, 0.4H), 2.64-3.28 (m, 8H), 2.48-2.60 (m, 1.5H), 2.25-2.38 (m, 0.5H), 1.29-1.77 (m, 2.5H), 1.07-1.24 (m, 4.5H), 0.87-1.02 (m 6H); MS (ESMS) *m/z* 551.4, 553.2, 555.6 $(M+H)^+$, Cl_2 isotope pattern. .

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-piperazin-1-yl}-N-isopropyl-3-naphthalen-2-yl-propionamide: MS (ESMS) *e/z* 545.5 $(M+H)^+$

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: MS (ESMS) *e/z* 517.5 $(M+H)^+$

2-{4-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methylpropionamide.

The second aspect of Category III comprises compounds having the formula:



wherein R is a substituted phenyl unit as described herein above and non-limiting examples of R^1, R^{5a}, R^{5b}, R^{7a}, and R^8 are defined herein below in Table IX and in the examples which follow.

TABLE IX

No.	R^1	R^{5a}	R^{5b}	R^{7a}	R^8
816	methyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
817	ethyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
818	propyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
819	*iso*-propyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
820	cyclopropyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
821	cyclopropylmethyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
822	allyl	-H	-H	$-NH_2$	naphthylen-2-ylmethyl
823	methyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
824	ethyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
825	propyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
826	*iso*-propyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
827	cyclopropyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
828	cyclopropylmethyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
829	allyl	-H	-H	$-NH_2$	(2-chlorophenyl)methyl
830	methyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
831	ethyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
832	propyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
833	*iso*-propyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
834	cyclopropyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
835	cyclopropylmethyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
836	allyl	-H	-H	$-NH_2$	(3-chlorophenyl)methyl
837	methyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
838	ethyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
839	propyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
840	*iso*-propyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
841	cyclopropyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
842	cyclopropylmethyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
843	allyl	-H	-H	$-NH_2$	(4-chlorophenyl)methyl
844	methyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
845	ethyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
846	propyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
847	*iso*-propyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
848	cyclopropyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
849	cyclopropylmethyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl

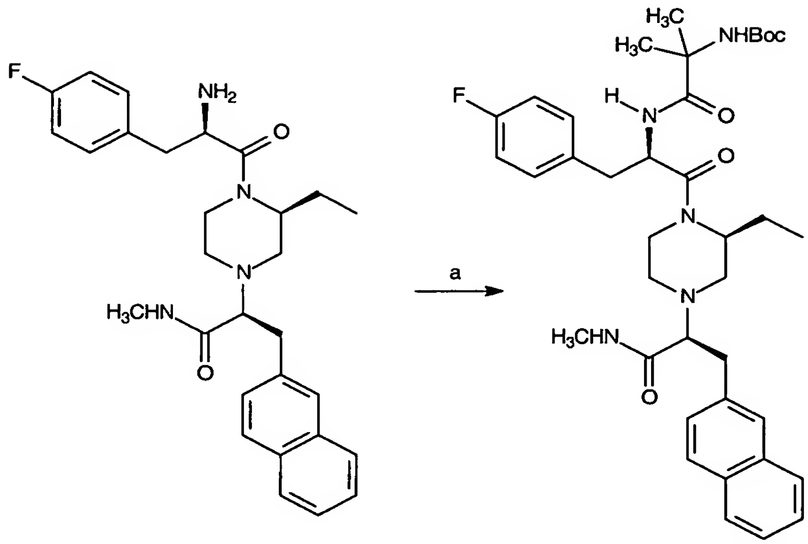
850	allyl	-H	-H	$-NH_2$	(2,4-dichlorophenyl)methyl
851	methyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
852	ethyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
853	propyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
854	*iso*-propyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
855	cyclopropyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
856	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
857	allyl	$-CH_3$	$-CH_3$	$-NH_2$	naphthylen-2-ylmethyl
858	methyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
859	ethyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
860	propyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
861	*iso*-propyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
862	cyclopropyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
863	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
864	allyl	$-CH_3$	$-CH_3$	$-NH_2$	(2-chlorophenyl)methyl
865	methyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
866	ethyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
867	propyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
868	*iso*-propyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
869	cyclopropyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
870	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
871	allyl	$-CH_3$	$-CH_3$	$-NH_2$	(3-chlorophenyl)methyl
872	methyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
873	ethyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
874	propyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
875	*iso*-propyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
876	cyclopropyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
877	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
878	allyl	$-CH_3$	$-CH_3$	$-NH_2$	(4-chlorophenyl)methyl
879	methyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
880	ethyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
881	propyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
882	*iso*-propyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
883	cyclopropyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
884	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl
885	allyl	$-CH_3$	$-CH_3$	$-NH_2$	(2,4-dichlorophenyl)methyl

886	methyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
887	ethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
888	propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
889	*iso*-propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
890	cyclopropyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
891	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
892	allyl	$-CH_3$	$-CH_3$	$-NHCH_3$	naphthylen-2-ylmethyl
893	methyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
894	ethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
895	propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
896	*iso*-propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
897	cyclopropyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
898	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
899	allyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2-chlorophenyl)methyl
900	methyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
901	ethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
902	propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
903	*iso*-propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
904	cyclopropyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
905	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
906	allyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(3-chlorophenyl)methyl
907	methyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
908	ethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
909	propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
910	*iso*-propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
911	cyclopropyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
912	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
913	allyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(4-chlorophenyl)methyl
914	methyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
915	ethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
916	propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
917	*iso*-propyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
918	cyclopropyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
919	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
920	allyl	$-CH_3$	$-CH_3$	$-NHCH_3$	(2,4-dichlorophenyl)methyl
921	methyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl

922	ethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
923	propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
924	*iso*-propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
925	cyclopropyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
926	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
927	allyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	naphthylen-2-ylmethyl
928	methyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
929	ethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
930	propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
931	*iso*-propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
932	cyclopropyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
933	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
934	allyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2-chlorophenyl)methyl
935	methyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
936	ethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
937	propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
938	*iso*-propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
939	cyclopropyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
940	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
941	allyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(3-chlorophenyl)methyl
942	methyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
943	ethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
944	propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
945	*iso*-propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
946	cyclopropyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
947	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
948	allyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(4-chlorophenyl)methyl
949	methyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
950	ethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
951	propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
952	*iso*-propyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
953	cyclopropyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
954	cyclopropylmethyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl
955	allyl	$-CH_3$	$-CH_3$	$-N(CH_3)_2$	(2,4-dichlorophenyl)methyl

The compounds of the second aspect of Category II can be suitably prepared by the procedure outlined herein below in Scheme XIII beginning with analogs such as compound **41**.

Scheme XIII



41

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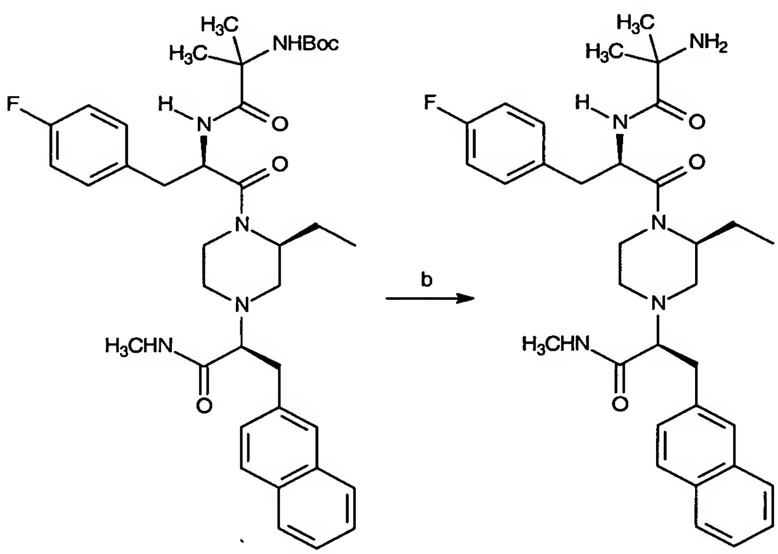
Reagents and conditions: (a) N-Boc-AIB, EDCI, HOBt, NMM; DMF; 0 °C, 18 hr.



46 47

Reagents and conditions: (b) HCl, dioxane; rt, 1 hr.

EXAMPLE 13

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazine-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (47)

Preparation of {1-[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl carbamoyl]-1-methyl-ethyl}-carbamic acid *tert*-butyl ester (46): 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide hydrochloride, **41**, (0.3g, 0.6 mmol) and *tert*-butyloxy-carbonyl-α-aminoisobutyric acid (AIB) (0.12g, 0.6 mmol) 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (0.22g, 1.1 mmol) and 1-hydroxybenzotriazole (0.1g, 0.7 mmol) are dissolved in anhydrous DMF (2.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.2 mL, 1.7 mmol) is added. The reaction mixture is placed in refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x30 mL). All organic layers are combined and washed with water (2x50 mL), and dried over Na_2SO_4. Solvent is removed *in vacuo* and the product is purified over silica (EtOAc/Hexane, 2/1) to afford 0.7 g of the desired compound. ^{1}H NMR ($CDCl_3$, δ): 7.80 – 7.58 (m, 4H), 7.42 – 7.22 (m, 3H), 7.20 – 7.00 (m, 2H), 6.98 – 6.50 (m, 2H), 5.40 –4.98 (m, 1.5H), 4.70 – 3.90 (m, 1H), 3.75 – 3.02 (m, 3.5H), 3.00 – 2.56 (m, 7H), 2.42 – 2.35 (m, 1H), 2.18 – 1.95 (m, 2.5H), 1.50 – 1.12 (m, 18H), .095 – 0.75 (m, 3H); ^{13}C NMR, δ 174.4, 172.1, 171.9, 170.3, 169.6, 163.7, 162.0, 154.6, 137.3, 133.7, 132.3, 131.4, 130.8, 128.1, 127.8, 127.6, 126.2, 125.6, 115.7, 115.4, 115.2, 80.0, 70.2, 56.7, 55.3, 50.9, 50.0, 49.9, 41.8, 39.5, 38.5, 37.9, 32.7, 32.4, 28.5, 28.3, 26.1, 25.5, 25.3, 23.1, 22.1, 10.6, 10.1.

Preparation of 2-{4-[2-(2-amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazine-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (47): {1-[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl carbamoyl]-1-methyl-ethyl}-carbamic acid *tert*-butyl ester, **46**, (0.4g, 0.6 mmol) is dissolved in 4M hydrogen chloride in dioxane (12 mL) and stirred at room temperature for 1 hour. 1,2- dichloro-ethane (12 mL) is added. The organic layers are concentrated *in vacuo* gives the crude HCl salt of product which is then purified by preparative HPLC to the TFA salt of product (0.28g, 0.35 mmol, 62% yield). A small amount of product is converted into the free base by treating with $NaHCO_3$ to obtain NMR spectra. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 – 8.15 (m, 1H), 7.82 – 7.75 (m, 4H), 7.45 – 7.15 (m, 6H), 7.00 – 6.95 (m, 2H), 5.12 – 4.98 (m, 1H), 4.52 (s, 0.5H), 4.32 (d, J = 8.3Hz, 0.5H), 3.65 – 3.28 (m, 3H), 3.08 – 2.50 (m, 10H), 2.35 – 2.20 (m, 1H), 1.88 – 1.58 (m, 5H), 1.32 (d, J = 3.34Hz, 3H), 1.15 (d, J = 18.4Hz, 4H), 0.8 m,3H); ^{13}C NMR, ($CDCl_3$, 300 MHz) δ 177.0, 172.3170.7, 170.0, 165.0, 161.5, 137.6, 133.9, 132.5, 131.5, 131.4, 128.4, 128.3, 128.0, 127.8, 127.7, 126.4, 125.8, 115.9, 115.7, 115.5, 70.8, 55.5, 51.3, 50.9, 49.9, 39.8, 38.1, 32.6, 29.3, 26.3, 23.3, 22.5, 10.9, 10.4; HRFAB(positive) m/e 576.3349 calculated for $C_{33}H_{42}FN_5O_3$ $(M+H)^+$, Found 576.3339

The following are non-limiting examples of procedures for forming other compounds which comprise the second aspect of Category III.

Preparation of 2-{4-[2-(2-amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide: 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-naphthalen-2-yl-propionamide HCl (0.22 g, 0.4 mmol) and t-butyloxycarbonyl-α-aminoisobutyric acid (AIB) (0.09 g, 0.5 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (0.17g, 0.9 mmol) and 1-hydroxybenzotriazole (0.07g, 0.5 mmol) are dissolved in anhydrous DMF (2.5 mL). This reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.14 mL, 1.3 mmol) is added. This reaction mixture is placed in a refrigerator for overnight. EtOAc (25 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL), the organic layers combined, washed with water (2 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.22 g (77% yield) of the desired product which is used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 – 7.64 (m, 4H), 7.45 – 7.30 (m, 3H), 7.20 – 7.10 (2H), 6.95 – 6.85 (m, 2H), 6.65 – 6.32 (m, 1H), 5.50 – 5.02 (m, 2H), 4.78 – 4.00 (m, 1H), 3.70 – 3.10 (m, 3H), 3.02 – 2.64 (m, 6H), 2.50 – 2.35 (m, 1H), 2.15 – 1.76 (m, 1H), 1.55 – 1.21 (m, 18H), 0.75 – 0.65 (m, 3H); ^{13}C NMR, ($CDCl_3$, 300 MHz) δ 174.5, 174.4, 174.0, 170.0, 169.8, 163.7, 160.4, 155.0, 137.0, 133.6, 132.3, 131.4, 131.3, 131.2, 131.0, 130.8, 128.1, 127.8, 127.6, 126.6, 126.2, 125.6, 125.3, 118.4, 115.8, 115.7, 115.6, 115.5, 115.2, 110.8, 80.0, 70.2, 69.9, 56.9, 56.7, 55.4, 51.5, 51.2, 51.0, 50.1, 49.9, 41.8, 39.6, 37.8, 32.6, 28.5, 28.3, 26.7, 26.0, 25.6, 23.1, 22.2, 10.7, 10.1.

The crude product obtained above (0.22g, 0.33 mmol) is dissolved in 4M hydrogen chloride in dioxane (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added. The solution is concentrated *in vacuo* to afford a residue which is purified by preparative HPLC (w/TFA for salt exchange) to give afford 0.17 g (64% yield) of the desired product. A small amount of product was converted into free base by treating with $NaHCO_3$ to obtain NMR spectra. ^1H NMR ($CDCl_3$, δ): 8.18 – 8.02 (m,1H), 7.78 – 7.58 (m, 4H), 7.40 – 7.25 (2H), 7.12 – 7.04 (m, 2H), 6.98 – 6.80 (2H), 6.46 (s, 0.5H), 6.15 (s, 0.5H), 5.66 – 5.45 (m, 1H), 5.10 – 4.82 (m, 1H), 4.49 (br s, 0.5H), 4.28 (d, J = 13.0 Hz, 0.5H), 3.60 – 3.12 (m, 3H), 3.00 – 2.58 (m, 5H), 2.51 – 2.39 (m, 1H), 2.28 – 2.00 (1H), 1.80 0 1.43 (m, m, 5H), 1.32 – 1.00 (m, 7H), 0.75 – 0.63 (m, 3H). HRFAB(positive) m/e 562.3193 calculated for $C_{32}H_{40}FN_5O_3$ $(M+H)^+$, Found 562.3216.

Preparation of 2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methyl-propionamide trifluoroacetate: Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methylpropionamide trifluoroacetate (0.3g, 0.43 mmol) and t-butyloxycarbonyl-

α-aminoisobutyric acid (AIB) (88 mg, 0.43 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (124 mg, 0.65 mmol) and 1-hydroxybenzotriazole (117 mg, 0.86 mmol) are dissolved in anhydrous DMF (2.5 mL). This reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.25 mL, 2.3 mmol) is added. This reaction mixture is placed in a refrigerator for overnight. EtOAc (25 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL), the organic layers combined, washed with water (2 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.3 g of the desired product which is used without further purification.

The crude product obtained above is dissolved in TFA/DCM/H_2O (1/2/0.1, 10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added. The solution is concentrated *in vacuo* to afford a residue which is purified by preparative HPLC (w/TFA for salt exchange) to give afford 0.167 g (59% yield) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 – 7.41 (m, 2H0, 7.32 – 7.27 (m, 2H), 7.17 – 7.00 (m, 3H), 5.16 (t, J = 8.1 Hz, 1H), 4.43 (br s, 0.5H), 4.28 (d, J = 13.5 Hz, 0.5H), 3.95 (d, J = 14.1 Hz, 0.5H), 3.63 (m, 0.5H), 3.42 – 3.21 (m, 8H), 3.22 – 2.81 (m, 6H), 2.84 – 2.66 (m, 3H), 2.52 – 2.43 (m, 2H), 2.20 – 2.13 (m, 1H), 1.82 – 1.66 (m, 2H), 1.60 – 1.42 (m, 6H), 0.80 0 0.72 (m, 3H). HRFAB(positive) m/e 594.241399 calculated for $C_{29}H_{38}Cl_2FN_5O_3$ $(M+H)^+$, Found 594.240266.

Preparation of 2-{4-[2-(2-amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-methyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide trifluoroacetate: 2-{4-[2-Amino-3-(4-fluoro-pnenyl)-propionyl}-3-methyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide (505mg, 0.71 mmol) and t-butyloxycarbonyl-α-aminoisobutyric acid (AIB) (144mg, 0.71 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (200mg, 1.07 mmol) and 1-hydroxybenzotriazole (193mg, 1.42 mmol) are dissolved in anhydrous DMF (2.0 mL). This reaction mixture is cool to 0 °C then N-methylmorpholine (0.3 mL, 2.7 mmol) is added. This reaction mixture is placed in a refrigerator for overnight. EtOAc (25 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL), the organic layers combined, washed with water (2 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.31 g of the desired product which is used without further purification.

The crude product obtained above is dissolved in TFA/DCM/H2O (1/2/0.1, 8 mL) and stirred at room temperature for 1hour. 1,2-dichloroethane (8 mL) is added and the solution is concentrated *in vacuo* to afford a residue which is purified by preparative HPLC (w/TFA for salt exchange) to give afford 0.250 g (59% yield) of the desired product. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 – 7.30 (m, 4H), 7.21 – 7.18 (m, 2H), 7.12 – 7.06 (m, 2H), 5.10 (t, J = 7.8 Hz, 1H), 4.77 (br s, 0.5H), 4.40 (d, J = 12.6 Hz, 0.5H), 4.10 –3.95 (m, 1H), 3.61 – 3.42 (m, 2H), 3.35 – 3.32 (m, 2H), 3.26 – 3.25 (m, 1.5H), 3.15 – 2.90 (m, 4.5H), 2.78 – 2.56 (m, 6H), 2.00 – 1.95 (m, 0.5H), 1.59 (s,

4H), 1.50 (br s, 3.5H), 1.41 (br s, 1.5H), 1.27 – 1.23 (m, 1.5H); ^{13}C NMR δ 174.0, 173.0, 172.0, 165.5, 162.2, 162.0, 137.2, 134.1, 132.9, 132.3, 130.0, 117.0, 116.7, 71.1, 58.5, 56.5, 52.3, 50.9, 50.2, 50.0, 46.5, 41.6, 38.8, 38.0, 35.1, 26.3, 24.6, 24.2, 17.0, 15.9. HRFAB(positive) m/e 546.264721 calculated for $C_{28}H_{37}ClFN_5O_3$ $(M+H)^+$, Found 546.262559.

The following are non-limiting examples of compounds which comprise the second aspect of Category III.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-methyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz δ): 7.47 – 7.42 (m,2H), 7.30 (br s, 2H), 7.18 – 7.06 (m, 3H), 5.11 – 5.04 (m, 1H), 4.34 – 4.30 (m, 0.5H), 3.98 – 3.93 (m, 1H), 3.36 – 3.34 (m, 6H), 3.11 – 2.90 (m, 5.5H), 2.69 – 2.30 (m, 4H), 1.98 – 1.84 (0.5H), 1.60 (s, 3H), 1.51 – 1.48 (m, 3H), 1.36 – 1.22 (m, 3H), 1.11 – 1.09(m, 1.5H). HRFAB(positive) m/e 580.225749 calculated for $C_{28}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 580.225133.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3-chlorophenyl)-N-methyl-propionamide HCl. ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.23 (m, 5H), 7.12 (m, 1H), 6.99 (m, 2H), 5.08 (m, 1H), 4.54-4.29 (m, 1H), 4.00-3.79 (m, 1H), 3.62-3.41 (m, 6H), 3.02 (m, 4H), 2.54, 2.50 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.32 (m, 1H), 1.93 (m, 1H), 1.62 (m, 1H), 1.54, 1.51, 1.42 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.11 (m, 1H), 0.86 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.2, 172.8, 172.1, 171.7, 167.6, 164.4, 162.8, 138.1, 135.7, 133.8, 132.6, 132.5, 131.5, 130.8, 129.2, 129.0, 116.8, 116.7, 116.5, 116.4, 74.2, 70.7, 70.3, 70.2, 69.4, 69.2, 68.3, 67.5, 67.1, 64.7, 64.5, 62.8, 62.3, 62.1, 58.5, 58.3, 54.6, 53.8, 53.0, 52.2, 52.0, 50.7, 50.4, 40.0, 38.8, 37.7, 36.5, 34.4, 32.8, 32.2, 26.3, 24.4, 24.3, 24.1, 20.4, 20.2, 18.5, 15.6, 14.6, 14.1; MS *m/z* (ESI): 574 (M + H, 100), 608 (M + 2 + H, 30).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide HCl: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.46-7.31 (m, 6H), 7.15 (m, 2H), 5.27 (m, 1H), 4.70-4.45 (m, 1H), 4.14 (m, 1H), 3.87-3.51 (m, 6H), 3.21 (m, 4H), 2.73, 2.70 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.42 (m, 1H), 2.07 (m, 1H), 1.73, 1.60 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.25 (m, 2H), 1.05 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.5, 172.0, 168.8, 165.5, 162.2, 135.8, 135.2, 134.9, 134.1, 132.8, 132.7, 132.6, 130.3, 116.8, 116.5, 74.0, 72.9, 71.0, 62.6, 58.6, 53.3, 52.3, 40.5, 39.1, 37.9, 34.5, 33.1, 32.5, 26.5, 24.6, 24.3, 20.7, 20.4, 14.4; MS *m/z* (ESI): 574 (M + H, 100), 576 (M + 2 + H, 37).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2-chlorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.83 (m, 1H), 7.47 (m, 5H), 7.25 (m, 2H), 5.35 (m, 1H), 4.84-4.52 (m, 1H), 4.19-3.90 (m, 1H), 3.76-3.62 (m, 1H), 3.48-2.92 (m, 9H), 2.86, 2.82 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.50-2.05 (m, 1H), 1.87 (m, 1H), 1.77, 1.70, 1.64 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.26 (m, 2H), 1.07 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.0, 172.9, 172.0, 171.8, 171.5, 171.4, 165.4, 162.2, 137.3, 136.8, 135.6, 134.3, 134.1, 133.5, 133.4, 132.9, 132.8, 132.7, 131.0, 130.0, 129.8, 128.4, 128.3, 117.0, 116.7, 116.4, 69.3, 58.5, 55.9, 54.9, 53.7, 52.4, 51.0, 50.4, 42.5, 39.3, 39.2, 38.1, 33.4, 33.2, 33.0, 32.5, 26.3, 24.6, 24.5, 24.3, 20.7, 20.6, 14.6; MS *m/z* (ESI): 574 (M + H, 100), 576 (M + 2 + H, 30).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2,4-dichlorophenyl)-N-methyl-propionamide trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.44 (m, 1H), 7.28 (m, 4H), 7.05 (m, 2H), 5.14 (m, 1H), 4.51-4.30 (m, 1H), 3.98-3.66 (m, 1H), 3.48-3.36 (m, 1H), 3.23-2.82 (m, 8H), 2.69 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.55 (m, 1H), 2.19-1.78 (m, 1H), 1.64 (m, 1H), 1.57 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.07 (m, 2H), 0.86 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.3, 173.2, 172.8, 172.5, 172.0, 165.4, 162.2, 136.7, 136.3, 134.7, 134.6, 134.5, 134.3, 134.1, 132.9, 132.8, 132.7, 130.5, 130.4, 69.1, 69.0, 58.5, 56.1, 55.0, 53.9, 52.4, 51.3, 42.8, 39.4, 38.2, 33.1, 32.9, 32.7, 32.6, 26.3, 24.6, 24.5, 24.3, 20.6, 14.6; MS *m/z* (ESI): 608 (M + H, 100), 610 (M + 2 + H, 30).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-4-(4-chlorophenyl)-N-methyl-butyramide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.13 (m, 6H), 6.87 (m, 2H), 4.96 (m, 1H), 4.43-4.10 (m, 1H), 3.85-3.70 (m, 1H), 3.53-3.10 (m, 4H), 3.01-2.81 (m, 4H), 2.63 (bs, 3H), 2.50 (m, 2H), 2.08 (m, 2H), 1.79-1.70 (m, 2H), 1.43, 1.31 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 0.96-0.74 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.5, 172.0, 169.0, 165.4, 162.2, 140.4, 134.0, 133.7, 132.8, 132.7, 131.5, 130.1, 116.8, 116.5, 69.7, 69.3, 58.5, 54.5, 52.9, 52.3, 50.9, 40.4, 37.9, 32.4, 30.5, 30.2, 27.8, 26.7, 24.6, 24.3, 20.4, 14.4; MS *m/z* (ESI): 588 (M + H, 100), 590 (M + 2 + H, 37).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-methyl-piperazin-1-yl}-3-(2-fluorophenyl)-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.29-7.09 (m, 8H), 5.11 (m, 1H), 4.70-4.30 (m, 1H), 4.00 (m, 1H), 3.50 (m, 1H), 3.17-3.00 (m, 7H), 2.67 (bs, 5H), 2.38-1.90 (m, 1H), 1.60, 1.52, 1.49 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.33 (m, 1H), 1.06 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ

173.0, 172.1, 171.6, 165.5, 164.7, 162.2, 161.5, 134.1, 133.2, 132.9, 130.3, 125.6, 117.0, 116.7, 116.4, 69.8, 58.5, 56.8, 56.4, 52.3, 51.3, 46.9, 42.2, 38.9, 38.6, 38.1, 29.4, 29.1, 26.3, 24.6, 24.3, 17.0, 16.0; MS *m/z* (ESI): 530 (M + H, 100).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2-fluorophenyl)-N-methyl-propionamide: ^1H NMR (300MHz, CD_3OD) δ 0.861 (m, 3H), 1.027 (m, 2H), 1.445, 1.508, 1.627 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.545 (t, 1H), 2.655, 2.696 (2 singlets, 3H, C<u>H</u>$_3$NHC(O), rotamers), 3.082 (m, 5H), 3.440 (t, 1H), 3.674 (m, 1H), 3.959 (d, 1H, J=13.8), 4.282 (d, 1H, J=13.5), 4.905 (m, 1H), 5.131 (m, 1H), 7.069 (m, 4H), 7.271 (m, 4H) ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 43.059, 44.958, 45.830; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.4, 164.8, 162.7, 162.2, 161.5, 134.3, 164.0, 133.2, 132.8, 132.7, 130.3, 129.9, 126.6, 125.5, 117.0, 116.7, 116.4, 91.8, 69.9, 58.8, 56.1, 55.1 54.0, 52.3, 51.3, 43.1, 39.6, 38.2, 33.1, 32.6, 29.3, 26.2, 24.7, 24.5, 24.3, 20.6, 14.6; MS *m/e* 558 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3-fluorophenyl)-N-methyl-propionamide: ^1H NMR (300MHz, CD_3OD) δ 1.113 (m, 3H), 1.380 (m, 2H), 1.720, 1.743, 1.816 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.680 (t, 1H), 2.854, 2.900 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.281 (m, 5H), 3.352 (m, 3H), 3.492 (t, 1H), 3.845 (t, 1H), 4.333 (d, 1H), 4.600 (d, 1H), 4.863 (m, 1H), 5.389 (m, 1H), 7.266 (m, 5H), 7.519 (m, 3H) ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 44.806, 47.319, 47.342; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.9, 132.8, 132.6, 131.4, 131.3, 126.6, 117.5, 117.2, 117.0, 116.7, 116.6, 116.4, 114.7, 114.5, 114.4, 114.3, 71.1, 71.0, 56.2, 55.0, 53.9, 52.3, 43.1, 39.6, 39.4, 38.1, 35.6, 35.2, 33.1, 32.3, 26.2, 24.6, 24.5, 24.3, 14.6; MS *m/e* 560 (M+1); MS *m/e* 560 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-fluorophenyl)-N-methyl-propionamide: ^1H NMR (300MHz, CD_3OD) δ 0.895 (m, 3H), 1.183 (m, 2H), 1.454, 1.513, 1.585 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.630, 2.669 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.0461 (m, 6H), 3.195 (m, 2H), 3.480 (m, 1H), 4.607 (m, 1H), 5.164 (m, 1H), 7.041 (m, 4H), 7.220 (m, 2H), 7.313 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 43.995, 44.249, 46.696, 47.232; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.4, 162.2, 135.4, 134.7, 134.2, 132.8, 132.7, 132.5, 132.4, 117.1, 116.7, 116.5, 116.4, 116.2, 113.6, 71.3, 58.5, 54.9, 53.7, 52.4, 42.3, 38.1, 34.9, 34.6, 33.1, 32.6, 26.3, 24.6, 24.5, 24.3, 20.7, 20.6, 14.5; MS *m/e* 560 (M+1)

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-difluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.887 (m, 3H), 1.108 (m, 2H), 1.350, 1.515, 1.583 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 2.293 (t, 1H), 2.649, 2.691 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.051 (m, 5H), 3.166 (m, 3H), 3.325 (m, 2H), 3.715 (m, 1H), 4.029 (d, 1H), 4.327 (d, 1H), 5.161 (m, 1H), 7.035 (m, 3H), 7.170 (m, 2H), 7.298 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 44.732; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 162.5, 162.0, 134.3, 132.8, 132.7, 127.2, 119.6, 119.4, 118.5, 118.3, 117.0, 116.6, 116.4, 71.1, 58.5, 56.0, 55.0, 53.9, 52.3, 51.1, 42.8, 39.3, 38.1, 35.0, 33.2, 32.7, 26.2, 24.6, 24.5, 24.2, 20.6, 14.6; MS *m/e* 578 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(2,5-difluorophenyl)-N-methyl-propionamide: ^{1}H NMR (300MHz, CD_3OD) δ 0.852 (m, 3H), 1.055 (m, 2H), 1.397 (m, 1H), 1.765 (m, 1H), 1.988 (m, 1H), 2.360 (m, 1H), 2.510 (m, 1H), 2.632, 2.700 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.869 (m, 3H), 3.071 (m, 4H), 4.249 (m, 1H), 4.502 (m, 1H), 5.167 (m, 1H), 7.043 (m, 5H), 7.293 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 37.110, 41.494, 45.143, 45.873; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.8, 132.7, 119.1, 117.0, 116.7, 116.4, 69.6, 61.4, 56.2, 55.0, 54.1, 52.1, 51.5, 43.3, 39.7, 38.6, 33.2, 32.6, 31.6, 29.1, 26.3, 25.3, 20.6, 14.6; MS *m/e* 676 (M+1).

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-piperazin-1-yl}-N-isopropyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (300 MHz, CD_3OD) δ 7.73-7.91 (m, 3H), 7.69 (s, 1H), 7.42-7.55 (m, 2H), 7.21-7.42 (m, 3H), 6.94-7.18 (m, 2H), 5.09-5.31 (m, 1H), 4.57-4.78 (m, 1H), 4.32-4.49 (m, 0.5H), 4.04-4.21 (m, 0.5H), 3.76-4.20 (m, 1H), 3.52-3.76 (m, 1H), 3.15-3.42 (m, 5H), 2.88-3.10 (m, 3H), 2.50-2.83 (m, 1H), 2.14-2.30 (m, 0.5H), 1.62-1.85 (m, 1H), 1.53-1.62 (m, 3H), 1.42-1.53 (m, 3H), 1.18-1.41 (m, 1H), 0.98-1.14 (m, 3H), 0.58-0.84 (m, 3.5H), 0.25-0.58 (m, 2.5H), -0.18-0.09 (m, 2H); ^{13}C NMR (75 MHz, MeOD) δ 173.08, 172.77, 172.25, 171.52, 170.25, 169.51, 165.42, 162.76, 162.20, 136.31, 135.36, 134.31, 134.17, 132.81, 132.71, 129.60, 129.02, 128.89, 127.59, 127.15, 117.03, 116.73, 116.68, 116.39, 71.13, 58.50, 56.27, 54.60, 54.03, 52.59, 52.38, 51.53, 50.17, 42.81, 42.39, 39.32, 38.97, 37.99, 36.12, 35.82, 35.16, 24.63, 24.30, 23.00, 22.61, 22.51, 9.27, 9.10, 5.63, 4.79; MS (ESMS) *e/z* 630.8 $(M+H)^+$.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-cyclopropylmethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.92 (m, 3H), 7.69 (s, 1H), 7.40-7.58 (m, 2H), 7.18-7.40 (m, 3H), 6.95-7.16 (m, 2H), 5.08-5.30 (m, 1H), 4.62-4.77 (m, 0.5H), 4.32-4.46 (m, 0.5H), 4.04-4.18 (m, 0.5H), 3.81-3.94 (m, 0.5H), 3.64-3.75 (m, 0.5H), 3.48-3.61 (m, 0.5H), 2.85-3.40 (m, 8H), 2.68-2.79 (m, 0.5H),

2.43-2.68 (m, 3H), 1.99-2.11 (m, 0.5H), 1.12-1.78 (m, 8H), 0.48-0.62 (m, 0.5H), 0.21-0.48 (m, 2.5H), -0.21-0.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.11, 172.78, 172.19, 172.02, 171.51, 136.58, 136.07, 135.36, 134.31, 132.79, 129.44, 129.04, 128.91, 127.60, 127.07, 117.06, 116.77, 116.67, 116.39, 71.24, 58.50, 56.40, 54.56, 54.18, 52.55, 52.37, 51.55, 50.17, 49.74, 42.41, 39.38, 39.01, 36.03, 35.84, 35.66, 35.08, 26.33, 24.63, 24.54, 24.30, 24.24, 9.23, 9.07, 5.62, 5.55, 4.70; MS (ESMS) *e/z* 602.6 $(M+H)^+$.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-(2-fluoroethyl)-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.39-7.48 (m, 2H), 7.25-7.34 (m, 2H), 7.12-7.21 (m, 1H), 6.95-7.12 (m, 2H), 5.08-5.22 (m, 1H), 4.20-4.58 (m, 3H), 3.93-4.02 (m, 0.66H), 3.68-3.78 (m, 0.33H), 3.38-3.60 (m, 3H), 2.71-3.20 (m, 8H), 2.49-2.63 (m, 1H), 1.84-1.94 (m, 0.33H), 1.62-1.72 (m, 0.66H), 1.40-1.59 (m, 7H), 0.94-1.36 (m, 2H), 0.83-0.93 (m, 3H); MS (ESMS) *m/z* 640.6, 642.6, 644.5 $(M+H)^+$, Cl_2 isotope pattern.

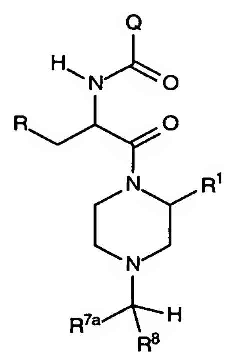
2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methyl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.38-7.4(m, 2H), 7.23-7.45 (m, 2H), 3.97-7.18 (m, 3H), 5.05-5.20 (m, 1H), 4.44-4.55 (m, 0.66H), 4.27 (d, J = 13.2Hz, 0.33H), 3.94 (d, J=13.2Hz, 0.66H), 3.59-3.70 (m, 0.33H), 2.74-3.28 (m, 8H), 2.71 (s, 1.25H), 2.67 (s, 1.75H), 2.36-2.49 (m, 1H), 2.06-2.20 (m, 0.33H), 1.25-1.73 (m, 8.66H), 0.94-1.22 (m, 2H), 0.86 (t, J = 6.9Hz, 3H); MS (ESMS) *m/z* 608.4, 610.6, 612.3 $(M+H)^+$, Cl_2 isotope pattern.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-isopropyl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.38-7.49 (m, 2H), 7.24-7.36 (m, 2H), 6.98-7.21 (m, 3H), 5.10-5.24 (m, 1H), 4.47-4.58 (m, 0.66H), 4.24-4.35 (m, 0.33H), 3.84-4.15 (m, 1.66H), 3.68-3.78 (m, 0.33H), 2.75-3.32 (m, 7H), 2.43-2.57 (m, 1.60H), 2.20-2.33 (m, 0.4H), 1.85-1.95 (m, 0.40H), 1.64-1.77 (m, 0.60H), 1.41-1.61 (m, 7H), 0.83-1.30 (m, 12H); MS (ESMS) *m/z* 636.4, 638.7, 640.8 $M+H)^+$, Cl_2 isotope pattern.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-(2-fluoroethyl)-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz with rotamers) δ 7.49-7.36 (m, 6H), 7.24 (m, 2H), 5.33 (m, 1H), 4.76-4.38 (m, 3H), 4.22-3.93 (m, 1H), 3.72-3.53 (m, 3H), 3.36-3.08 (m, 6H), 2.90 (m, 2H), 2.58-2.13 (m, 1H), 1.92 (m, 1H), 1.74, 1.69, 1.66, 1.61 (4 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.27 (m, 3H), 1.07 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz with rotamers) δ 173.0, 172.9, 172.0, 171.5, 165.5,

162.2, 138.4, 137.8, 134.3, 134.0, 132.8, 132.7, 132.4, 129.9, 117.0, 116.7, 116.4, 84.4, 82.2, 71.0, 58.5, 55.8, 55.0, 53.9, 52.4, 51.0, 42.5, 41.3, 41.0, 39.3, 39.1, 38.1, 35.1, 34.7, 33.2, 32.7, 24.6, 24.5, 24.3, 20.7, 20.6, 14.6; MS *m/z* (ESI): 606 (M + H, 100), 608 (M + 2 + H, 37); *Anal.* Calcd for $C_{35}H_{44}ClF_8N_5O_7 \cdot 0.5$ TFA: C, 48.52; H, 5.03; N, 7.86. Found: C, 48.43; H, 4.82; N, 7.84.

The third aspect of Category III comprises compounds having the formula:



wherein R is a substituted phenyl unit as described herein above and non-limiting examples of R^1, R^{7a}, R^8, and Q are defined herein below in Table XII and in the examples which follow.

TABLE XII

No.	R^1	R^{7a}	Q	R^8
956	methyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
957	ethyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
958	propyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
959	*iso*-propyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
960	cyclopropyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
961	cyclopropylmethyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
962	allyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	naphthylen-2-ylmethyl
963	methyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
964	ethyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
965	propyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
966	*iso*-propyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
967	cyclopropyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
968	cyclopropylmethyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
969	allyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(2-chlorophenyl)methyl
970	methyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
971	ethyl	$-C(O)NHCH_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl

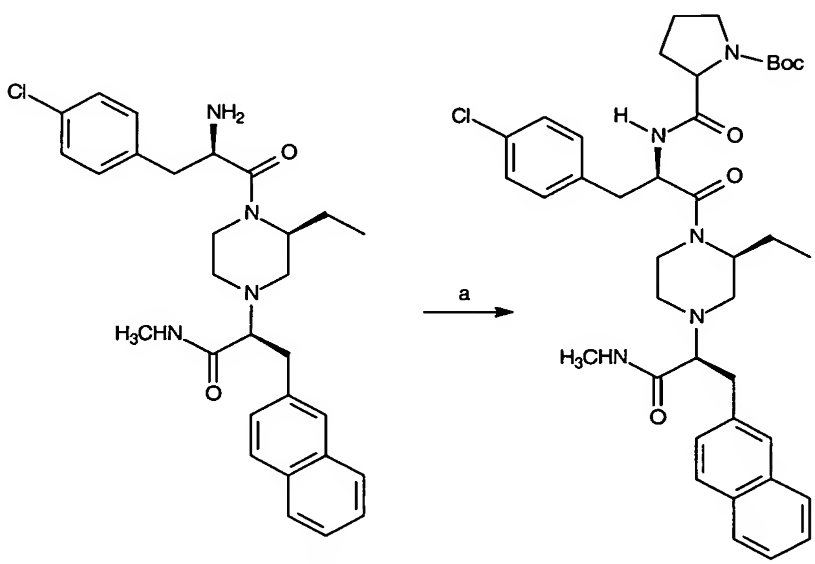
972	propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
973	*iso*-propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
974	cyclopropyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
975	cyclopropylmethyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
976	allyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(3-chlorophenyl)methyl
977	methyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
978	ethyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
979	propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
980	*iso*-propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
981	cyclopropyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
982	cyclopropylmethyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
983	allyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(4-chlorophenyl)methyl
984	methyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
985	ethyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
986	propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
987	*iso*-propyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
988	cyclopropyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
989	cyclopropylmethyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
990	allyl	-C(O)NHCH$_3$	pyrrolidin-2-yl	(2,4-dichlorophenyl)methyl
991	methyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
992	ethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
993	propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
994	*iso*-propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
995	cyclopropyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
996	cyclopropylmethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
997	allyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	naphthylen-2-ylmethyl
998	methyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
999	ethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1000	propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1001	*iso*-propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1002	cyclopropyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1003	cyclopropylmethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1004	allyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2-chlorophenyl)methyl
1005	methyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1006	ethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1007	propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl

1008	*iso*-propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1009	cyclopropyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1010	cyclopropylmethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1011	allyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(3-chlorophenyl)methyl
1012	methyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1013	ethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1014	propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1015	*iso*-propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1016	cyclopropyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1017	cyclopropylmethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1018	allyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(4-chlorophenyl)methyl
1019	methyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1020	ethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1021	propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1022	*iso*-propyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1023	cyclopropyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1024	cyclopropylmethyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1025	allyl	-C(O)NHCH$_3$	1-aminocycloprop-1-yl	(2,4-dichlorophenyl)methyl
1026	methyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1027	ethyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1028	propyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1029	*iso*-propyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1030	cyclopropyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1031	cyclopropylmethyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1032	allyl	-C(O)NHCH$_3$	azetidin-2-yl	naphthylen-2-ylmethyl
1033	methyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1034	ethyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1035	propyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1036	*iso*-propyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1037	cyclopropyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1038	cyclopropylmethyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1039	allyl	-C(O)NHCH$_3$	azetidin-2-yl	(2-chlorophenyl)methyl
1040	methyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1041	ethyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1042	propyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1043	*iso*-propyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl

1044	cyclopropyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1045	cyclopropylmethyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1046	allyl	-C(O)NHCH$_3$	azetidin-2-yl	(3-chlorophenyl)methyl
1047	methyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1048	ethyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1049	propyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1050	*iso*-propyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1051	cyclopropyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1052	cyclopropylmethyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1053	allyl	-C(O)NHCH$_3$	azetidin-2-yl	(4-chlorophenyl)methyl
1054	methyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1055	ethyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1056	propyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1057	*iso*-propyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1058	cyclopropyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1059	cyclopropylmethyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl
1060	allyl	-C(O)NHCH$_3$	azetidin-2-yl	(2,4-dichlorophenyl)methyl

The compounds of the third aspect of Category III can be suitably prepared by the procedure outlined herein below, utilizing final analogs from the first aspect of this Category as starting points, for example, compound 45, as depicted in Scheme XIV herein below.

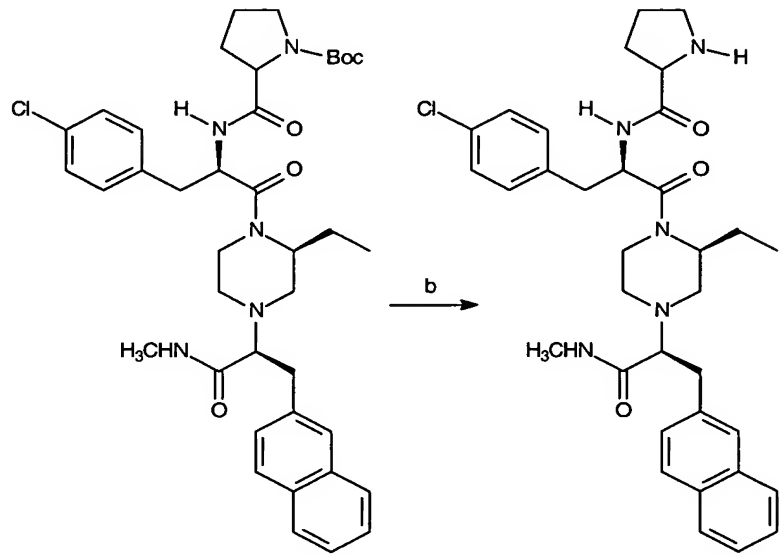
Scheme XIV



45

48

Reagents and conditions (a) N-Boc-proline, EDCI, HOBt, NMM, DMF; 0 °C, 18 hr.



48 49

Reagents and conditions (b) 4 N HCl, dioxane; rt 1 hr.

EXAMPLE 14

Pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-[2-ethyl-4-(1-methyl-carbamoyl-2-naphthalen-2-yl-ethyl) piperazin-1-yl]-2-oxo-ethyl]-amide trifluoroacetate (49)

Preparation of 2-[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl) piperazin-1-yl]-(4-chlorobenzyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (48): 2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide HCl, **45**, (0.5 g, 0.7 mmol) and Boc-L-proline (0.17 g, 0.78 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.19 g, 1.4 mmol) and 1-hydroxybenzotriazole (0.16g, 0.86 mmol) are dissolved in anhydrous DMF (2.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.6 mL, 5.3 mmol) is added. This reaction mixture is placed in a refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL). All organic layers are combined and washed with water (2 x 50 mL), and dried over Na_2SO_4. Solvent is removed *in vacuo* to afford 0.5 g of the desired product.

Preparation of pyrrolidine-2-carboxylic acid {1-(4-chlorobenzyl)-2-[2-ethyl-4-(1-methyl-carbamoyl-2-naphthalen-2-yl-ethyl) piperazin-1-yl]-2-oxo-ethyl]-amide trifluoroacetate (49): 2-[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl) piperazin-1-yl]-(4-chlorobenzyl)-2-oxo-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, **48**, (0.5 g)

is dissolved in 4M hydrogen chloride in dioxane (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added. The organic layers are combined and concentrated *in vacuo* and the crude product is purified by preparative HPLC to afford the desired product. A small amount of product is converted into free base by treating with $NaHCO_3$ to obtain NMR spectra. ^{1}H NMR ($CDCl_3$, 300 MHz δ): 8.22 – 8.17 (m, 1H), 7.82 – 7.47 (m, 4H), 7.47 – 7.35 (m, 3H), 7.29 – 7.12 (m, 3H), 6.61 – 6.45 (m, 1H), 5.13 (quartet, J = 8.1Hz, 0.5H), 5.02 (quartet, J = 6.9 Hz, 0.5H), 4.45 (br s, 0.5H), 4.34 – 4.30 (m, 0.5H), 3.75 –3.70 (m, 1H), 3.66 – 3.63 (m, 2H), 3.50 (br s, 1H), 3.40 – 3.15 (m, 3H), 3.02 –2.83 (m, 5H), 2.81 – 2.75 (m, 4H), 2.50 – 2.11 (m, 4H), 1.83 – 1.75 (m, 2H), 1.70 – 1.44 (4H), 0.79 – 0.73 (m, 2H); ^{13}C NMR, δ1174.7, 172.1, 170.4, 137.7, 135.2, 133.7, 132.2, 131.3, 131.1, 129.0, 128.7, 128.2, 127.9, 127.7, 126.2, 125.6, 70.8, 60.7, 55.2, 52.1, 51.3, 50.9, 50.3, 50.0, 49.5, 49.2, 47.5, 41.9, 39.9, 38.7, 38.7, 32.4, 31.8, 31.1, 30.9, 26.2, 23.3, 22.4, 14.5, 10.8, 10.0; HRFAB(positive) m/e 604.305443 Calculated for $C_{34}H_{42}ClN_5O_3$ $(M+H)^+$, Found 604.308207.

The following are non-limiting examples of procedures for preparing other analogs encompassed with the third aspect of Category III.

Preparation of Pyrrolidine-2-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(1-fluorobenzyl)-2-oxo-ethyl]-amide: 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide HCl, **41**, (0.3 g, 0.6 mmol) and Boc-L-proline (0.13 g, 0.6 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.13 g, 1.1 mmol) and 1-hydroxybenzotriazole (0.16 g, 0.86 mmol) are dissolved in anhydrous DMF (2.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.2 mL, 1.7 mmol) is added. This reaction mixture is placed in a refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL). All organic layers are combined and washed with water (2 x 50 mL), and dried over Na_2SO_4. Solvent is removed *in vacuo* to afford 0.39 g of the desired product.

The crude product obtained above is dissolved in 4M hydrogen chloride in dioxane (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added. The organic layers are concentrated *in vacuo* gives the crude HCl salt of the product which was then purified by preparative HPLC to give the TFA salt of product (0.2g, 0.23 mmol, 42% yield). A small amount of product was converted into the free base by treating with $NaHCO_3$ to obtain NMR spectra. ^{1}H NMR ($CDCl_3$, 300 MHz δ): 7.75 – 7.55 (m, 4H), 7.40 – 7.22 (m, 3H), 7.12 – 7.02 (m,2H), 6.92 – 6.80 (m, 2H), 6.50 – 6.28 (m, 1H), 5.10 – 4.90 (m, 1H), 4.58 – 4.20 (m, 1H), 3.79 – 3.20 (m, 4H), 3.10 – 2.60(m, 9H), 2.50 – 2.30 (m, 1H), 2.22 – 1.50 (m, 11H), 0.80 – 0.68 (m, 3). HRFAB(positive) m/e 588.3350 calculated for $C_{34}H_{42}FN_5O_3$ $(M+H)^+$.

Preparation of 5-oxo-pyrrolidine-2-carboxylic acid[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazine-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoro-acetate: 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide hydrochloride (0.78 g, 0.83 mmol) and L-pyroglutamic acid (0.11g, 0.83 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.19 g, 1.0 mmol) and 1-hydroxy-benzotriazole (0.22 g, 1.66 mmol) are dissolved in anhydrous DMF (4 mL). The reaction mixture is cooled to 0 °C, then N-mathylmorpholine (0.6 mL, 5.46 mmol) is added. The reaction mixture is stirred for 3-4 hrs. EtOAc (30 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL). The organic layers are combined, washed with water (2 x 50 mL), dried over Na_2SO_4, then concentrated *in vacuo* to provide a crude product which is purified by preparative HPLC to afford 0.14 g of the desired product. ^1H NMR ($CDCl_3$, 300 MHz δ): 7.83 – 7.78 (m, 3H), 7.69 (s, 1H), 7.48 – 7.45 (m, 2H), 7.35 – 7.28 (m, 3H), 7.10 – 7.00 (m, 2H), 5.20 – 5.11 (m, 1H), 4.69 (br s, 0.5H), 4.50 (d, J = 13.9 Hz, 0.5H), 4.19 – 4.17 (m, 1.5H), 3.96 – 3.85 (m, 1H), 3.74 (t, J = 8.4 Hz, 0.5H), 3.58 – 3.54 (m, 0.5H), 3.44 – 3.26 (m, 8H), 3.11 – 2.91 (m, 3H), 2.85 – 2.74 (m, 0.5H), 2.57 – 2.51 (m, 3H), 2.36 – 2.22 (m, 3H), 2.12 – 2.09 (m, 0.5H), 3.96 – 1.85 – 1.76 (m, 1.5H), 1.73 – 1.61 (m, 1H), 0.87 – 0.76 (m, 3H); ^{13}C NMR, ($CDCl_3$, 75 MHz) δ1182.0, 176.0, 175.0, 173.0, 172.0, 168.0, 166.0, 163.0, 135.4, 134.5, 134.3, 134.1, 134.0, 133.0, 132.9, 132.8, 129.9, 129.7, 129.6, 129.1, 129.0, 128.6, 127.8, 127.5, 127.3, 117.1, 116.8, 116.5, 71.4, 71.0, 58.1, 56.2, 53.6, 53.4, 51.9, 51.5, 51.0, 40.6, 39.8, 38.3, 37.6, 35.45, 30.9, 27.2, 26.5, 24.1, 23.4, 11.0; HRFAB(positive) m/e 602.314258 calculated for $C_{34}H_{40}FN_5O_4$ $(M+H)^+$.

Preparation of azetidine-2-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide. 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide, **41**, (0.78g, 0.83 mmol) and Boc-L-azetidine-2-carboxylic acid (0.17 g, 0.83 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.19 g, 1.0 mmol) and 1-hydroxybenzotriazole (0.22 g, 1.66 mmol) are dissolved in anhydrous DMF (2 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.6 mL, 5.46 mmol) is added. The reaction mixture is stirred for 4 hrs. EtOAc (30 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x30 mL). All organic layers are combined and washed with water (2x50 mL), and dried over Na_2SO_4. The solution is concentrated *in vacuo* to afford the desired product which is used without further purification.

2-[2-[2-ethyl-4-(1-methyl-carbamoyl-2-naphthalen-2-ylethyl)-piperazin-1-yl-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-azetidine-1-carboxylic acid *tert*-butyl ester is dissolved in DCM/TFA/H2O (2/1/0.1) (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane

(10 mL) is added. The organic layers are combined, washed with water (2 x 50 mL), dried over Na_2SO_4, then concentrated *in vacuo* to provide a crude product which is purified by preparative HPLC to afford 32 mg of the desired product. (HCS3621-118). ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.90 – 7.84 (m, 3H), 7.75 (s, 1H), 7.54 – 7.51 (m, 2H), 7.43 – 7.34 (m, 3H), 7.18 – 7.08 (m, 2H), 5.30 – 5.25 (m, 1H), 5.06 – 5.00 (m, 1.5H), 4.59 (bs s, 0.5H), 4.43 (d, J = 14.2 Hz, 0.5H), 4.21 – 4.11 (m, 1.5H), 4.00 – 3.91 (m, 1H), 3.80 – 3.69 (m, 1H), 3.55 (t, J = 7.5 Hz, 0.5H), 3.40 – 3.38 (m, 3H), 3.32 – 3.20 (m, 4H), 3.17 – 2.75 (m, 6H), 2.73 – 2.67 (m, 1.5H), 2.51 – 2.24 (m, 1.5H), 2.02 – 1.54 (m, 2.5H), 0.88 – 0.77 (m, 3H); ^{13}C NMR, ($CDCl_3$, 75 MHz) δ 172.0, 169.0, 165.4, 162.3, 136.8, 136.1, 135.4, 134.2, 133.9, 133.0, 132.8, 132.7, 129.5, 129.4, 129.0, 128.9, 127.6, 127.1, 127.0, 117.1, 116.8, 116.5, 71.3, 60.2, 57.1, 54.2, 52.4, 52.0, 51.9, 50.5, 50.0, 49.9, 49.7, 49.1, 45.5, 42.2, 39.7, 38.5, 35.9, 35.7, 26.3, 25.3, 24.0, 23.4, 11.1; HRFAB(positive) m/e 574.319344 calculated for $C_{33}H_{40}FN_5O_3$ $(M+H)^+$, Found 574.320780.

Preparation of azetidine-3-carboxylic acid [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoro-acetate: 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide, **41**, (0.78g, 0.83 mmol) and Boc-azetidine-3-carboxylic acid (0.17g, 0.83 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.19 g, 1.0 mmol) and 1-hydroxybenzotriazole (0.22 g, 1.66 mmol) are dissolved in anhydrous DMF (2 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.6 mL, 5.46 mmol) is added. The reaction mixture is stirred for 3-4 hrs. EtOAc (30 mL) and water (100 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x30 mL). All organic layers are combined and washed with water (2x50 mL), and dried over Na_2SO_4. The solution is concentrated *in vacuo* to afford the desired product which is used without further purification.

3-[2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-ylethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-azetidine-1-carboxylic acid *tert*-butyl ester is dissolved in DCM/TFA/H2O (2/1/0.1) (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added, the solvent removed *in vacuo* to give a residue which is purified by preparative HPLC to afford 300 mg of the desired product. ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.71 – 7.64 (m, 3H), 7.55 – 7.54 (m, 1H), 7.40 – 7.31 (m, 2H), 7.26 – 7.13 (m,3H), 6.97 – 6.87 (m, 3), 5.00 (t, J = 7.7 Hz, 1H), 4.46 (br s, 0.5H), 4.32 (d, J = 13.8 Hz, 0.5H), 4.08 – 3.86 (m, 6H), 3.68 – 3.63 (m, 0.5H), 3.60 – 3.49 (m, 1.5H), 3.47 – 3.41 (m, 0.5H), 3.25 – 3.00 (m, 2H), 3.14 – 3.03 (m, 3H), 2.98 – 2.65 (m, 5.5H), 2.54 – 2.35 (m, 3H), 1.77 – 1.56 (m, 1.5H), 1.55 – 1.36 (m, 0.5), 0.69 – 0.58 (m, 3H); ^{13}C NMR, ($CDCl_3$, 75 MHz) δ 175.0, 173.0, 172.0, 166.0, 163.0, 135.4, 134.1, 133.0, 132.9, 132.8, 132.7, 129.7, 129.5, 129.4, 129.0, 128.9, 128.8, 128.7, 127.7, 127.6, 127.3, 127.1, 117.1, 116.8, 116.5, 71.3, 71.2, 56.8, 53.9, 53.4, 52.2, 52.0, 51.9, 50.7, 50.3, 50.1, 50.0, 49.1, 41.6,

39.7, 38.4, 37.0, 35.7, 26.4, 24.0, 23.4, 11.1; HRFAB(positive) m/e 574.317945 calculated for $C_{33}H_{40}FN_5O_3$ $(M+H)^+$, Found 574.319344.

The following are non-limiting examples of other analogs which comprise the third aspect of Category III.

N-[2-{4-[2-(4-Chlorophenyl)-1-methylcarbamoyl-ethyl]-2-methyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide trifluoroacetate: ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 8.85 (s, 2H), 8.20 - 7.00 (m, 10H), 5.40 – 5.30 (m, 1H), 4.50 – 4.05 (m, 2H), 3.70 – 2.88 m, 8H), 2.80 – 2.65 (m, 4H), 1.90 – 1.05 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 175.0, 167.0, 149.1, 148.0, 146.0, 138.0, 134.0, 133.0, 132.4, 130.1, 124.8, 116.9, 71.6, 55.7, 52.8, 51.2, 50.3, 50.0, 49.7, 46.4, 41.0, 39.0, 38.3, 34.9, 26.4, 17.1, 15.9. HRFAB(positive) m/e 566.233421 calculated for $C_{30}H_{33}ClFN_5O_3$ $(M+H)^+$, Found 566.231196.

N-[2-{4-[2-(3,4-Dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-ethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz): δ 8.80 (s, 1H), 7.97 (s, 1H), 7.39 – 7.30 (m, 5H), 7.10 – 7.02 (m, 4H), 5.40 (br s, 1H), 4.60 (br s, 1H), 4.45 – 4.38 (m, 0.5H), 4.18 – 4.10 (m, 0.5H), 3.70 (br, s, 0.5H), 3.60 – 3.52 (m, 1H), 3.42 – 2.85 (m, 9H), 2.78 – 2.60 (m, 3H), 2.40 – 2.30 (1H), 1.98 – 1.78 (m, 2H), 1.62 – 1.52 (m, 1H), 0.78 – 0.74 (m, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 175.0, 174.0, 172.0, 166.5, 165.5, 162.2, 148.2, 148.0, 140.2, 139.1, 134.1, 133.7, 133.0, 132.9, 132.7, 132.3, 132.0, 131.8, 130.8, 125.2, 117.1, 116.8, 116.6, 91.0, 70.7, 57.1, 53.8, 53.4, 53.0, 52.6, 52.2, 50.8, 50.3, 50.0, 49.7, 41.8, 39.5, 38.8, 38.3, 34.4, 26.4, 24.0, 23.4, 11.1. HRFAB(positive) m/e 614.210099 calculated for $C_{31}H_{34}Cl_2FN_5O_3$ $(M+H)^+$, Found 614.210894.

Pyrrolidine-2-carboxylic acid[2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-methyl-piperazine-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz): δ 7.65 – 7.60 (m, 2H), 7.49 (s, 2H), 7.36 – 7.25 (m, 3H), 5.33 – 5.30 (m, 1.5H), 4.92 (br s, 0.5H), 4.56 – 4.42 (m, 1.5H), 4.21 – 4.18 (m, 1H), 3.66 – 3.62 (m, 1H), 3.59 – 3.48 (m, 5H), 3.45 – 3.17 (m, 7H), 2.85 – 2.82 (m, 4H), 2.56 (br s, 1.5H), 2.25 – 2.02 (m, 3.5H), 1.52 – 1.50 (m, 1.5H), 1.32 – 1.26 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz): δ 174.0, 170.0, 165.5, 162.2, 140.3, 139.8, 133.9, 133.5, 132.9, 131.8, 130.7, 117.0, 116.7, 116.5, 113.3, 70.9, 70.8, 61.4, 56.6, 56.4, 52.0, 51.2, 50.3, 50.0, 49.7, 49.4, 47.7, 46.8, 42.0, 39.2, 38.5, 34.9, 34.7, 31.6, 26.3, 25.3, 17.1, 16.0. HRFAB(positive) m/e 592.225749 calculated for $C_{29}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 592.224706.

Pyrrolidine-2-carboxylic acid[2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-methyl-piperazine-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, δ): 7.32 – 7.30 (m, 4H), 7.21 – 7.18 (m, 2H), 7.10 – 7.03 (m, 2H), 5.18 – 5.10 (m, 1H), 4.79 (br s, 0.5H), 4.42 (d, J = 13.5Hz, 0.5H), 4.25 (t, J =7.5 Hz, 1H), 4.10 – 4.00 (m, 1.5H), 3.60 – 3.57 (m, 1H), 3.50 – 3.43 (m, 1H), 3.42 – 3.27 (m, 6H), 3.20 – 2.89 (m, 4.5H), 2.82 – 2.75 (m, 0.5H), 2.63 (d, J = 9.0 Hz, 4H), 2.46 – 2.30 (m, 1H), 2.08 – 1.75 (m, 4H), 1.38 (d, J = 5.7 Hz, 1.5H), 1.12 (d, J = 5.7 Hz, 1.5H); ^{13}C NMR δ 174.0, 170.0, 165.5, 162.5, 162.2, 137.4, 134.3, 133.9, 132.9, 132.5, 130.0, 119.9, 117.0, 116.8, 116.5, 116.0, 71.0, 61.4, 56.3, 52.0, 50.9, 50.3, 50.0, 49.7, 47.7, 46.5, 41.5, 39.1, 38.4, 38.0, 35.1, 31.6, 26.3, 25.3, 17.0, 16.0. HRFAB(positive) m/e 558.264721 calculated for $C_{29}H_{37}ClFN_5O_3$ $(M+H)^+$, Found 558.263046.

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-ethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoracetate. ^{1}H NMR (CD_3OD, δ): 7.45 – 7.41 (m, 2H), 7.32 – 7.28 (m, 2H), 7.17 – 7.01 (m, 3H), 5.22 - 5.15 (m, 1H), 4.49 (br s, 0.5H), 4.35 – 4.21 (m, 1.5), 4.02 (d, J = 13.2 Hz, 0.5H), 3.67 (br s, 0.5), 3.46 – 3.25 (m, 5H), 3.20 – 2.84 (m, 6H), 2.80 – 2.52 (m, 5H), 2.38 – 2.26 (m, 1H), 2.05 – 1.54 (m, 6H0, 0.82 – 0.73 (m, 3H); ^{13}C NMR δ 173.0, 172.0, 171.0, 170.0, 169.0, 165.4, 162.2, 140.8, 140.1, 133.9, 133.4, 132.9, 131.8, 131.7, 130.7, 117.0, 116.7, 116.4, 70.8, 61.4, 57.3, 54.4, 52.6, 52.1, 52.0, 50.3, 50.0, 49.7, 49.4, 49.1, 47.7, 42.5, 39.6, 39.1, 38.5, 34.7, 34.5, 31.6, 26.3, 25.2, 24.0, 23.4, 11.1. HRFAB(positive) m/e 606.241399 calculated for $C_{30}H_{38}Cl_2FN_5O_3$ $(M+H)^+$, Found 606.240332.

1-Amino-Cyclopropanecarboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-ethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, δ): 7.55 – 6.90 (m, 7H), 5.18 – 4.22 (m, 3.5H), 4.02 – 3.90 (m, 0.5H), 3.70 – 2.15 (m, 17H), 1.88 – 1.12 (m, 6H), 0.80 – 0.6 (m, 2H). HRFAB(positive) m/e 592.225749 calculated for $C_{29}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 592.224973.

N-[2-{4-[2-(4-Chlorophenyl)-1-(2-fluoroethylcarbamoyl)-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide HCl: ^{1}H NMR (CD_3OD, with rotamers) δ 9.11 (br s, 2H), 8.42 (br s, 2H), 7.46-7.32 (m, 6H), 7.11 (m, 2H), 5.41 (m, 1H), 4.72-4.11 (m, 4H), 3.94-3.17 (m, 12H), 2.40-0.98 (m, 7H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.9, 167.9, 165.5, 162.3, 145.4, 135.0, 133.8, 132.9, 132.6, 130.4, 130.0, 126.9, 116.9, 116.7, 84.2, 82.0, 71.1, 54.4, 53.3, 52.9, 51.4, 50.7, 41.5, 41.2, 40.4, 38.1, 34.4, 33.2, 32.6, 20.4, 14.4; MS *m/z* (ESI): 626 (M + H, 100), 628 (M + 2 + H, 37).

N-[2-{4-[2-(2,4-Dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide HCl: ^{1}H NMR (CD_3OD, with rotamers) δ 8.85 (d, 2H, *J* = 5.0 Hz), 8.20 (d, 2H, *J* = 5.5 Hz), 7.31 (s, 1H), 7.19-7.11 (m, 4H), 6.86 (m, 2H), 5.15 (m, 1H), 4.45-4.14 (m, 1H), 3.78 (m, 1H), 3.16 (m, 1H), 3.34 (m, 4H), 3.07-2.99 (m, 5H), 2.43, 2.38 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.10-0.70 (m, 7H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.9, 168.0, 165.5, 165.4, 162.3, 151.1, 145.0, 136.6, 136.0, 134.6, 134.1, 133.8, 132.9, 130.9, 129.1, 127.0, 117.2, 116.9, 116.7, 69.2, 68.7, 54.5, 53.9, 53.0, 51.7, 51.2, 40.3, 39.2, 38.1, 37.2, 33.1, 32.5, 32.2, 26.6, 20.7, 20.4, 14.4; MS *m/z* (ESI): 628 (M + H, 100), 630 (M + 2 + H, 70).

Pyrrolidine-2-carboxylic acid [2-{4-[3-(4-chlorophenyl)-1-methylcarbamoyl-propyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.11 (m, 6H), 6.85 (m, 2H), 4.97 (m, 1H), 4.43-4.07 (m, 2H), 3.87-3.68 (m, 1H), 3.49-3.08 (m, 4H), 3.00-2.80 (m, 4H), 2.61 (bs, 3H), 2.47 (m, 2H), 2.17-2.03 (m, 4H), 1.82-1.44 (m, 6H), 1.00-0.72 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.0, 170.0, 168.8, 165.5, 140.3, 133.8, 132.8, 131.5, 130.1, 116.8, 116.5, 70.0, 61.4, 54.4, 51.9, 51.1, 47.7, 40.3, 38.2, 32.4, 31.5, 30.4, 26.7, 25.3, 20.4, 14.4; MS *m/z* (ESI): 600 (M + H, 100), 602 (M + 2 + H, 37).

2-{4-[2-Aminosulfonyl amino-3-(4-fluorophenyl)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) 6.80~8.00 (m, 11H), 4.62 (m, 1H), 4.41 (m, 1H), 3.91 (m, 1H), 2.90~3.50 (m, 10H), 2.46 (d, J=2.7 Hz, 3H), 1.58 (m, 2H), 0.80~1.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz), 171.58, 166.73, 138.61, 132.85, 131.34, 131.29,131.18, 128.98, 128.49, 127.93, 127.83, 126.82, 126.56, 116.09, 115.80, 68.56, 53.79, 52.28, 47.97, 47.54, 38.92, 38.40, 34.09, 30.50, 26.40, 19.10, 13.54; MS (ES-MS) *m/z* 584 (M+1).

Pyrrolidine-2-carboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(2-fluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-2-oxo-ethyl)-amide: ^{1}H NMR (300MHz, CD_3OD) δ 0.84 (t, 3H), 1.055 (m, 2H), 1.39 (m, 2H), 1.83 (m, 5H), 2.36 (m, 2H), 2.67, 2.70 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.02 (m, 8H), 3.95 (m, 1H, J=12.3), 4.22 (m, 1H), 4.49 (m, 1H), 5.17 (m, 1H), 7.07 (m, 4H), 7.27 (m, 4H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 42.67, 42.69, 44.86, 45.59; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 133.2, 132.8, 129.9, 125.5, 117.0, 116.7, 116.4, 69.8, 61.4, 56.1, 55.0, 54.1, 52.0, 51.4, 50.2, 47.7, 43.1, 39.7, 38.6, 32.6, 31.6, 29.3, 29.0, 26.2, 25.3, 20.6, 14.6; MS *m/e* 572 (M+1).

Pyrrolidine-2-carboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(4-fluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-2-oxo-ethyl)-amide: ^{1}H NMR (300MHz, CD_3OD) δ 0.90 (t, 3H), 1.12 (m, 2H), 1.53 (m, 2H), 1.78 (m, 2H), 1.98 (m, 5H), 2.36 (m, 1H), 2.60,

2.64 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.85 (m, 1H), 3.05 (m, 8H), 3.33 (m, 8H), 3.55 (m, 1H), 4.24 (m, 1H), 4.74 (m, 1H), 5.19 (m, 1H), 7.05 (m, 4H), 7.22 (m, 2H), 7.31 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 44.92, 45.29, 45.38, 46.17; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.5, 162.9, 162.2, 134.9, 133.9, 132.8, 132.6, 132.5, 117.1, 116.7, 116.6, 116.5, 116.3, 71.3, 61.4, 55.5, 54.7, 52.0, 50.3, 41.8, 38.4, 34.8, 34.6, 33.2, 32.5, 31.6, 26.4, 25.3, 20.7, 20.5, 14.5; MS *m/e* 570 (M+1).

Pyrrolidine-2-carboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(3,4-difluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-2-oxo-ethyl)-amide: ^1H NMR (300MHz, CD_3OD) δ 0.929 (m, 3H), 1.179 (m, 2H), 1.53 (m, 2H), 1.776 (m, 2H), 1.97 (m, 5H), 2.34 (m, 2H), 2.63, 2.67 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.79 (m, 1H), 3.04 (m, 8H), 3.33 (m, 8H), 3.689 (m, 1H), 4.69 (m, 1H), 5.19 (m, 1H), 7.04 (m, 1H), 7.18 (m, 3H), 7.31 (m, 3H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 19.44, 19.98, 22.28, 22.61, 45.27, 46.08; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 171.6, 171.3, 169.4, 169.2, 164.4, 162.8, 162.3, 162.1, 133.7, 132.7, 132.6, 132.5, 132.5, 127.0, 119.4, 119.3, 119.3, 118.4, 118.2, 118.1, 116.7, 116.6, 116.4, 116.3, 70.7, 70.6, 61.1, 54.6, 51.8, 50.5, 49.9, 49.6, 49.4, 38.2, 34.5, 32.4, 31.3, 26.1, 25.0, 25.0, 20.3, 14.3; MS *m/e* 589 (M+1).

N-[2-{4-[2-(3,4-Difluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-isonicotinamide: ^1H NMR (300MHz, CD_3OD) δ 0.90 (t, 3H), 1.140 (m, 2H), 1.52 (m, 2H), 1.79 (m, 1H), 1.96 (m, 1H), 2.61, 2.67 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.03 (m, 3H), 3.22 (m, 5H), 3.33 (m, 3H), 3.78 (m, 1H), 4.77 (m, 1H), 5.33 (m, 1H), 7.12 (m, 5H), 7.35 (m, 2H), 8.16 (d, 2H, J=5.7, 2-pyr-H), 8.93 (d, 2H, J=4.2, 3-pyr-H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 22.322, 22.354, 22.787, 45.402, 46.214; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 165.5, 150.1, 149.9, 145.6, 145.4, 134.2, 132.9, 132.8, 132.7, 127.2, 124.2, 119.7, 119.4, 119.3, 118.7, 118.3, 118.2, 117.1, 116.8, 116.5, 114.6, 71.4, 71.1, 56.1, 54.4, 53.8, 52.7, 52.6, 51.1, 50.8, 42.7, 39.5, 38.4, 34.6, 33.3, 32.7, 26.3, 20.7, 20.6, 14.6; MS *m/e* 596 (M+1).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(2,5-difluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (300MHz, CD_3OD) δ 0.847 (m, 3H), 1.264 (m, 2H), 1.427 (m, 5H), 1.450 (m, 5H), 1.853 (m, 3H), 2.037 (m, 1H), 2.696, 2.732 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.944 (m, 3H), 3.466 (m, 3H), 3.750 (m, 1H), 4.210 (m, 2H), 5.280 (m, 1H), 7.049 (m, 5H), 7.294 (m, 2H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 37.012, 41.402, 44.910, 45.792; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.8, 117.0, 116.7, 116.4, 69.6, 58.5, 55.2, 52.3, 50.2, 38.2, 32.6, 26.2, 24.7, 24.3, 20.6, 14.6; MS *m/e* 688 (M+1).

4-Amino-cyclohexanecarboxylic acid [2-{4-[2-(3,4-difluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (300MHz, CD_3OD) δ 0.890 (m, 3H), 1.094 (m, 2H), 1.470 (m, 2H), 1.680 (m, 4H), 1.813 (m, 4H), 2.489 (m, 2H), 2.659, 2.776 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.894 (m, 2H), 3.012 (m, 3H), 3.989 (m, 1H), 4.295 (m, 1H), 4.531 (m, 1H), 5.112 (m, 1H), 7.024 (m, 3H), 7.159 (m, 2H), 7.294 (m, 3H); ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 18.657, 19.025, 21.450, 21.721, 44.742, 45.624; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 132.7, 127.1, 119.6, 119.3, 118.3, 116.9, 116.6, 116.3, 71.2, 56.0, 55.0, 54.1, 51.6, 51.1, 42.8, 40.8, 39.9, 385, 35.0, 33.2, 32.7, 28.6, 26.3, 26.0, 20.6, 14.6; HRMS *m/e* for $C_{33}H_{44}F_3N_5O_3$ (M+1) calc.: 616.347451, found: 616.349725.

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (300 MHz, MeOD, Rotamers) δ 7.39-7.48 (m, 2H), 7.24-7.36 (m, 2H), 6.99-7.20 (m, 3H), 5.08-5.26 (m, 1H), 4.48-4.60 (m, 0.66H), 4.18-4.38 (m, 1.33H), 3.95-4.07 (m, 0.66H), 3.64-3.74 (m, 0.33H), 3.21-3.32 (m, 1H), 2.76-3.19 (m, 6H), 2.71 (s, 1.4H), 2.66 (s, 1.6H), 1.59-2.10 (m, 3.7H), 1.35-1.54 (m, 1H), 0.99-1.28 (m, 2H), 0.83-0.93 (m, 3H); ^{13}C NMR (75 MHz, MeOD, Rotamers) δ 171.93, 171.62, 170.64, 169.72, 169.44, 165.46, 163.16, 162.68, 162.21, 161.71, 133.96, 133.61, 133.45, 132.90, 132.73, 132.24, 131.93, 131.80, 130.74, 117.04, 116.76, 116.47, 70.70, 70.63, 61.35, 55.66, 54.86, 53.98, 52.06, 51.98, 50.57, 49.99, 49.35, 47.73, 41.99, 39.65, 38.80, 38.47, 34.60, 34.47, 33.18, 32.55, 31.64, 26.38, 25.28, 20.67, 20.57, 14.55; MS (ESMS) *m/z* 620.4, 622.4, 624.6 $(M+H)^+$, Cl_2 isotope pattern.

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-isopropylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (300 MHz, MeOD, Rotamers) δ 7.39-7.50 (m, 2H), 7.24-7.36 (m, 2H)m, 7.00-7.21 (m, 3H), 5.11-5.28 (m, 1H), 4.48-4.59 (m, 0.6H), 4.17-4.36 (m, 1.4H), 3.84-4.05 (m, 1.6H), 3.70-3.81 (m, 0.4H), 2.76-3.26 (m, 8H), 2.46-2.63 (m, 1.4H), 2.22-2.41 (m, 1.6H), 1.62-2.28 (m, 4H), 1.42-1.57 (m, 1H), 0.83-1.37 (m, 12H); MS (ESMS) *m/z* 648.5, 650.6, 652.1 $(M+H)^+$, Cl_2 isotope pattern

Pyrrolidine-2-carboxylic acid [2-{4-[2-(3-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide dihydrochloride. ^{1}H NMR (CD_3OD, with rotamers) δ 7.10-6.80 (m, 8H), 4.98 (m, 1H), 4.42-3.97 (m, 3H), 3.73-3.30 (m, 7H), 2.88 (m, 4H), 2.40, 2.36 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.19 (m, 1H), 1.80-1.45 (m, 6H), 0.98-0.68 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.8, 169.5, 167.5, 165.4, 162.2, 138.3, 135.9, 133.9, 132.9, 132.8, 131.8,131.0, 129.5, 129.2, 117.1, 116.8, 116.5, 114.1, 74.5, 71.1,

70.6, 69.5, 62.6, 61.4, 54.7, 54.0, 53.5, 51.8, 51.2, 47.8, 40.2, 38.2, 34.7, 32.5, 31.6, 26.6, 25.3, 20.7, 20.4, 14.4; MS *m/z* (ESI): 586 (M + H, 100), 588 (M + 2 + H, 37).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide dihydrochloride. ^{1}H NMR (CD_3OD, with rotamers) δ 7.18 (m, 6H), 6.92 (m, 2H), 5.04 (m, 1H), 4.48-3.82 (m, 3H), 3.56-3.16 (m, 8H), 3.01 (m, 4H), 2.46, 2.42 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.23 (m, 1H), 1.89-1.61 (m, 4H), 1.30-1.00 (m, 3H), 0.77 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.8, 170.0, 168.0, 165.5, 162.2, 135.0, 134.9, 134.0, 132.9, 132.8, 132.7, 130.3, 117.1, 116.8, 116.5, 97.8, 97.5, 74.5, 71.1, 70.6, 69.5, 62.6, 61.4, 54.7, 52.1, 51.9, 51.1, 50.6, 47.8, 40.3, 38.3, 34.4, 32.5, 31.6, 26.6, 25.4, 20.7, 20.4, 14.4; MS *m/z* (ESI): 586 (M + H, 100), 588 (M + 2 + H, 30).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(2-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.29 (m, 1H), 7.05 (m, 5H), 7.85 (m, 2H), 4.95 (m, 1H), 4.33-4.19 (m, 1H), 4.00 (m, 1H), 3.83-3.50 (m, 1H), 3.32-3.14 (m, 1H), 3.06-2.65 (m, 10H), 2.48 (m, 1H), 2.44, 2.41 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.11 (m, 1H), 1.79-1.44 (m, 4H), 1.21 (m, 1H), 0.90 (m, 2H), 0.65 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.0, 172.5, 172.4, 172.0, 168.6, 168.5, 165.4, 162.3, 137.5, 137.0, 135.6, 134.0, 133.5, 133.4, 133.0, 132.8, 132.7, 131.0, 129.9, 129.8, 128.4, 128.3, 117.0, 116.7, 116.4, 69.4, 69.3, 61.4, 56.0, 54.8, 53.8, 52.1, 51.1, 47.7, 42.8, 39.7, 38.5, 33.5, 33.3, 33.1, 32.5, 31.6, 26.3, 25.3, 20.6, 14.6, ; MS *m/z* (ESI): 586 (M + H, 100), 588 (M + 2 + H, 30).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(2,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.45 (m, 1H), 7.28 (m, 4H), 7.06 (dd, 2H, J = 17.6, 8.8 Hz), 5.16 (m, 1H), 4.14-4.23 (m, 2H), 4.04-3.69 (m, 1H), 3.54-3.36 (m, 1H), 3.28-2.69 (m, 9H), 2.69, 2.65 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.35 (m, 2H), 1.98 (m, 4H), 1.63-1.41 (m, 2H), 1.07 (m, 2H), 0.86 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.5, 172.0, 171.9, 169.1, 169.0, 165.5, 162.3, 136.7, 136.4, 136.1, 134.8, 134.6, 134.5, 134.0, 133.9, 133.0, 132.9, 132.7, 130.5, 130.4, 128.6, 128.5, 117.0, 116.7, 116.4, 69.2, 69.0, 61.4, 56.1, 54.9, 54.0, 52.1, 51.2, 47.7, 42.8, 39.7, 39.3, 38.6, 33.2, 32.9, 32.7, 32.6, 31.6, 26.3, 25.3, 20.6, 14.6; MS *m/z* (ESI): 620 (M + H, 100), 622 (M + 2 + H, 70).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(4-chlorophenyl)-1-(2-fluoroethylcarbamoyl)-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.12-7.03 (m, 6H), 6.88 (m, 2H), 5.00 (m, 1H), 4.41-4.01 (m, 4H),

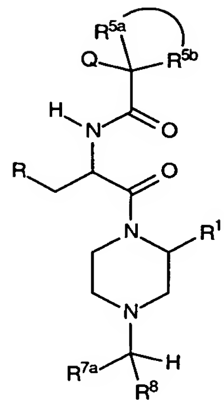
3.90-3.60 (m, 1H), 3.34-2.57 (m, 12H), 2.47-2.13 (m, 2H), 1.84-1.53 (m, 4H), 1.32 (m, 1H), 1.00 (m, 3H), 0.71 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.0, 171.7, 171.5, 169.0, 165.5, 162.2, 138.5, 137.9, 134.0, 133.8, 132.8, 132.7, 132.4, 129.9, 129.8, 117.0, 116.7, 116.4, 84.5, 82.3, 71.1, 61.4, 55.9, 54.9, 54.0, 52.1, 51.0, 47.7, 42.7, 41.3, 41.0, 39.6, 39.2, 38.5, 35.1, 34.7, 33.3, 32.7, 31.6, 25.3, 20.7, 20.6, 14.6; MS *m/z* (ESI): 618 (M + H, 100), 620 (M + 2 + H, 37).

Pyrrolidine-2-carboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(2-fluorophenyl)-1-methyl-carbamoyl-ethyl]-2-methyl-piperazin-1-yl}-2-oxo-ethyl)-amide · trifluoroacetate. ^1H NMR (CD_3OD, with rotamers) δ 7.27-7.03 (m, 8H), 5.13 (m, 1H), 4.69-4.30 (m, 1H), 4.24 (m, 1H), 3.99 (m, 1H), 3.49 (m, 2H), 3.16-3.00 (m, 8H), 2.65 (m, 5H), 2.38 (m, 1H), 2.00 (m, 4H), 1.30 (m, 1H), 1.05 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 171.9, 171.5, 169.6, 165.5, 164.7, 162.3, 161.5, 133.9, 133.3, 132.9, 130.2, 125.7, 117.0, 116.7, 116.4, 113.2, 69.9, 61.4, 56.7, 56.4, 52.0, 51.3, 47.8, 46.9, 42.2, 39.2, 38.5, 31.6, 29.3, 29.2, 26.3, 25.3, 17.1, 16.0; MS *m/z* (ESI): 542 (M + H, 100).

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-[2-methyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide: ^1H NMR (300 MHz, MeOD, Rotamers) δ 7.60-7.89 (m, 3H), 7.69 (s, 1H), 7.42-7.53 (m, 2H), 7.25-7.38 (m, 3H), 7.01-7.16 (m, 2H), 5.06-5.22 (m, 1H), 4.76-4.90 (m, 0.4H), 4.40-4.55 (m, 0.6H), 4.04-4.33 (m, 2H), 3.61-3.89 (m, 1H), 2.66-3.33 (m, 7H), 2.51-2.63 (m, 3H), 2.28-2.46 (m, 1H), 1.70-2.02 (m, 3H), 1.32-1.49 (m, 1.4H), 1.09-1.25 (m, 1.6H); ^{13}C NMR (75 MHz, MeOD, Rotamers) δ 172.40, 171.96, 170.75, 170.50, 169.73, 165.49, 162.79, 162.25, 135.37, 134.37, 133.90, 133.86, 132.90, 129.63, 129.50, 129.05, 128.94, 128.73, 127.66, 127.26, 117.01, 116.78, 116.53, 71.30, 61.35, 56.20, 52.01, 50.26, 50.51, 50.14, 47.75, 46.33, 41.18, 39.13, 38.36, 37,69, 35.82, 31.60, 26.38, 25.31, 17.03, 15.93; MS (ESMS) *m/z* 574.4 $(M+H)^+$.

Pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-[4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-amide. ^1H NMR ($CDCl_3$, 300 MHz) 7.42~7.89 (m, 6H), 7.19~7.34 (m, 3H), 6.96~7.10 (m, 2H), 4.00~4.90 (m, 6H), 3.30~3.90 (m, 8H), 2.80~3.20 (m, 3H), 2.50~2.75 (m, 3H), 2.36 (m, 1H), 1.60~2.10 (m, 5H), 1.25 (m, 2H), 0.95 (m, 3H); MS (ES-MS) *m/z* 602 (M+1).

A fourth aspect of Category III melanocortin receptor ligands relate to compounds wherein R^{5a} and R^{5b} are taken together to form a carbocyclic or heterocyclic ring having from 3 to 10 atoms, said compounds having the general scaffold with the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{5a}/R^{5b} ring, R^{7a}, R^8 and Q are defined herein below in Table XIII.

TABLE XIII

No.	R^1	R^{5a}/R^{5b} ring	Q	R^{7a}	R^8
1061	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1062	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1063	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1064	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1065	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1066	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1067	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1068	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1069	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1070	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1071	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1072	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1073	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1074	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1075	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1076	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1077	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1078	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1079	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1080	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1081	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1082	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl

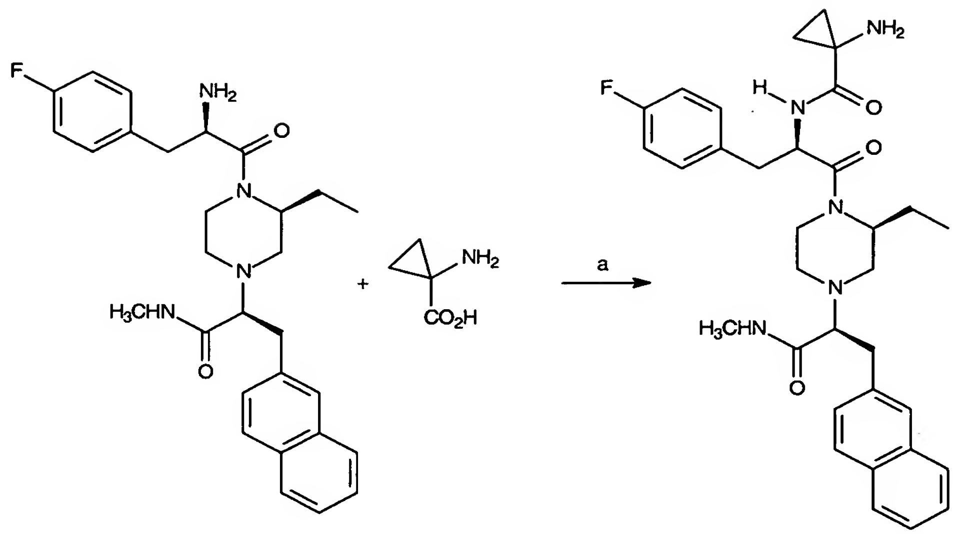
1083	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1084	$-CH_2CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1085	$-CH_2CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1086	$-CH_2CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1087	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1088	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1089	$-CH_2(C_3H_5)$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1090	$-CH_2(C_3H_5)$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1091	$-CH_2(C_3H_5)$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1092	$-CH_2(C_3H_5)$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1093	$-CH_2(C_3H_5)$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1094	$-CH_2(C_3H_5)$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1095	$-CH_2(C_3H_5)$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1096	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1097	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1098	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1099	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1100	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1101	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1102	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1103	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1104	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1105	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1106	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1107	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1108	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1109	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1110	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1111	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1112	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1113	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1114	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1115	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1116	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1117	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1118	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl

1119	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1120	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	naphthylen-2-ylmethyl
1121	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1122	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1123	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1124	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1125	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1126	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1127	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1128	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1129	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1130	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1131	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1132	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1133	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1134	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1135	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1136	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1137	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1138	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1139	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1140	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1141	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1142	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1143	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1144	$-CH_2CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1145	$-CH_2CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1146	$-CH_2CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1147	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1148	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1149	$-CH_2(C_3H_5)$	cyclopropyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1150	$-CH_2(C_3H_5)$	cyclobutyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1151	$-CH_2(C_3H_5)$	cyclopentyl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1152	$-CH_2(C_3H_5)$	azetidin-2-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1153	$-CH_2(C_3H_5)$	azetidin-3-yl	$-NH_2$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1154	$-CH_2(C_3H_5)$	cyclopropyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl

1155	$-CH_2(C_3H_5)$	cyclobutyl	$-NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1156	$-CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1157	$-CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1158	$-CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1159	$-CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1160	$-CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1161	$-CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1162	$-CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1163	$-CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1164	$-CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1165	$-CH_2CH_3$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1166	$-CH_2CH_3$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1167	$-CH_2CH_3$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1168	$-CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1169	$-CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1170	$-CH_2CH=CH_2$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1171	$-CH_2CH=CH_2$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1172	$-CH_2CH=CH_2$	cyclopentyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1173	$-CH_2CH=CH_2$	azetidin-2-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1174	$-CH_2CH=CH_2$	azetidin-3-yl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1175	$-CH_2CH=CH_2$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1176	$-CH_2CH=CH_2$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1177	$-CH_2CH_2CH_3$	cyclopropyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1178	$-CH_2CH_2CH_3$	cyclobutyl	$-NH_2$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1179	$-CH_2CH_2CH_3$	cyclopropyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl
1180	$-CH_2CH_2CH_3$	cyclobutyl	$-NHCH_3$	$-C(O)N(CH_3)_2$	(3,4-dichlorophenyl)methyl

The compounds of the fourth aspect of Category III can be suitably prepared by the procedure outlined herein below, utilizing final analogs from the first aspect of this Category as starting points, for example, compound 41, as depicted in Scheme XVII herein below.

Scheme XV



41

50

Reagents and conditions: (a) EDCI. HOBt, NMM, DMF; 0 °C, 18 hr.

EXAMPLE 15

<u>1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-ethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide (50)</u>

Preparation of 1-amino-cyclopropanecarboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-ethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide (50): Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-3-(3,4-dichlorophenyl)-N-methylpropionamide, **41**, (0.3g, 0.43 mmol) and 1-amino-cyclopropanecarboxylic acid (87mg, 0.43 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (124mg, 0.65 mmol) and 1-hydroxybenzotriazole (117mg, 0.86 mmol) are dissolved in anhydrous DMF (2.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.25 mL, 2.3 mmol) is added. The reaction mixture is placed in refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x30 mL). All organic layers are combined and washed with water (2x50 mL), and dried over Na_2SO_4. Solvent is removed *in vacuo* and the product dissolved in a mixture of trifluoroacetic acid, dichloro-methane, and water (1:2:0.1) and stirred at room temperature for 1 hour. 1,2-dichloroethane (10 mL) is added and the solvents are removed in vacuo and the resulting residue purified over prep HPLC to afford 232 mg (71% yield) of the desired compound. ^{1}H NMR (CD_3OD, 330 MHz): δ 7.55 – 6.90 (m, 7H), 5.18 – 4.22 (m, 3.5H), 4.02 – 3.90 (m, 0.5H), 3.70 – 2.15 (m, 17H), 1.88 – 1.12 (m, 6H), 0.80 – 0.6 (m, 2H). HRFAB(positive) m/e 592.225749 calculated for $C_{29}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 592.224973.

The following are non-limiting examples of compounds which comprise the fourth aspect of Category III.

1-Amino-cylopropanecarboxylic acid {2-{4-{2-(3,4-dichlorophenyl)-1-methyl-carbamoyl-ethyl]-2-methyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz)) δ 7.46 – 7.40 – (m, 2H), 7.26 – 7.05 (m, 5H), 5.11 – 5.07 (m, 1H), 4.31 (d J = 12.8 Hz, 0.5H), 4.01 – 3.92 (m, 1H), 3.44 – 3.38 (m, 0.5H), 3.35 – 3.33 (m, 4H), 3.11 – 2.95 (m, 8H), 2.68 – 2.66 (m, 5H), 2.33 – 2.29 (m, 1H), 1.80 – 1.32 (m, 6H). HRFAB(positive) m/e 578.210099 calculated for $C_{28}H_{34}Cl_2FN_5O_3$ $(M+H)^+$, Found 578.207967.

1-Amino-cylopropanecarboxylic acid {2-{4-{2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-methyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate: ^{1}H NMR (CD_3OD, 300 MHz)) δ 7.33 – 7.23 (m, 4H), 7.21 – 7.18 (m, 2H), 7.10 – 7.05 (m, 2H), 5.08 (t, J = 7.8 Hz, 1H), 4.77 (br s, 0.5H), 4.40 (d, J = 12.6 Hz, 0.5H), 4.05 – 4.00 (m, 1H), 3.68 – 3.60 (m, 0.5H), 3.50 – 3.40 (m, 0.5H), 3.34 – 3.24 (m, 3H), 3.20 – 2.80 (m, 8H), 2.66 – 2.60 (m, 4H), 1.98 – 1.90 (m, 0.5H), 1.69 – 1.60 (m, 1H), 1.55 – 1.40 (m, 5H), 1.13 – 1.00 (m, 1.5H); ^{13}C NMR (CD_3OD, 75 MHz)) δ 174.0, 173.0, 172.0, 171.0, 165.5, 162.5, 162.2, 162.0, 137.4, 134.0, 132.8, 132.4, 130.0, 116.8, 71.1, 56.3, 52.3, 50.9, 50.3, 50.0, 49.7, 46.4, 41.4, 38.7, 38.0, 36.7, 35.0, 26.4, 17.0, 15.9, 13.9. HRFAB(positive) m/e 544.249071 calculated for $C_{28}H_{35}ClFN_5O_3$ $(M+H)^+$, Found 544.248512.

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-(2-fluoroethylcarbamoyl)-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz)) δ 7.50-7.38 (m, 6H), 7.25 (m, 2H), 5.33 (m, 1H), 4.76-4.49 (m, 3H), 4.23-3.90 (m, 1H), 3.73-3.54 (m, 2H), 3.40-3.01 (m, 8H), 2.83 (m, 1H), 2.52-2.04 (m, 1H), 1.90-1.06 (m, 11H); ^{13}C NMR (CD_3OD, 75 MHz)) δ 172.2, 171.8, 171.5, 170.9, 165.5, 162.2, 138.5, 137.8, 134.2, 134.0, 133.8, 132.7, 132.6, 132.4, 129.9, 117.1, 116.7, 116.5, 84.5, 82.2, 71.0, 55.9, 54.9, 53.7, 52.3, 51.0, 42.5, 41.3, 41.0, 39.2, 38.0, 36.7, 35.1, 34.7, 33.2, 32.7, 20.8, 20.6, 14.6, 13.9, 13.8; MS *m/z* (ESI): 604 (M + H, 100), 606 (M + 2 + H, 37).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-(2-fluoroethylcarbamoyl)-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.50-7.40 (m, 6H), 7.27 (dd, 2H, *J* = 18.9, 10.1 Hz), 5.36 (m, 1H), 4.76-4.49 (m, 3H), 4.22-3.94 (m, 1H), 3.70-3.57 (m, 2H), 3.35-3.04 (m, 8H), 2.90 (s, 3H), 2.83 (m, 1H), 2.48-2.07 (m, 1H), 1.94-1.05 (m, 11H); ^{13}C NMR (CD_3OD, 75 MHz, with rotamers) δ 172.4, 172.0, 171.6, 169.6, 165.5, 162.4, 138.6, 138.0, 134.3, 132.8, 132.4, 129.9, 117.0, 116.7, 116.4, 113.7, 84.5, 82.3, 71.1, 55.9, 55.0, 53.8, 52.3, 51.1,

44.0, 42.6, 41.3, 41.0, 39.3, 39.1, 38.0, 35.1, 34.7, 33.3, 32.7, 20.6, 14.6, 13.8; MS *m/z* (ESI): 618 (M + H, 100), 620 (M + 2 + H, 37).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide · trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.39-7.09 (m, 8H), 5.22 (m, 1H), 4.66-4.38 (m, 1H), 4.14-3.75 (m, 1H), 3.56-2.89 (m, 10H), 2.75, 2.72 (2 singlets, 3H, CH_3NHC(O), rotamers), 2.37-0.95 (m, 11H); ^{13}C NMR (CD_3OD, 75 MHz, with rotamers) δ 172.5, 172.2, 171.8, 170.9, 170.5, 165.3, 162.2, 138.6, 137.8, 134.1, 132.7, 132.3, 129.9, 129.8, 117.1, 116.7, 116.5, 71.2, 55.9, 54.9, 53.7, 52.3, 50.9, 42.4, 39.2, 38.0, 36.7, 35.1, 34.8, 33.1, 32.6, 26.3, 20.7, 20.6, 14.6, 13.9, 13.8; MS *m/z* (ESI): 572 (M + H, 100), 574 (M + 2 + H, 37).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide · trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.46-7.16 (m, 8H), 5.30 (m, 1H), 4.77-4.47 (m, 1H), 4.24-3.87 (m, 1H), 3.74 (m, 1H), 3.43-3.04 (m, 8H), 2.86, 2.85 (2 singlets, 3H, $\underline{CH_3}$NHC(O), rotamers), 2.81, 2.77 (2 singlets, 3H, CH_3NHC(CH_2-CH_2)C(O), rotamers), 2.58-2.00 (lm, 1H), 1.83-1.02 (m, 11H); ^{13}C NMR (CD_3OD, 75 MHz, with rotamers) δ 172.1, 171.7, 171.2, 169.8, 165.5, 162.2, 138.4, 137.5, 134.2, 133.8, 132.8, 132.7, 132.4, 130.0, 129.8, 117.1, 116.8, 116.5, 71.1, 55.8, 54.9, 53.6, 52.3, 50.7, 44.1, 42.2, 39.1, 37.9, 35.0, 34.8, 33.3. 33.2, 32.6, 26.3, 20.7, 20.6, 14.5, 13.8, 13.6; MS *m/z* (ESI): 586 (M + H, 100), 588 (M + 2 + H, 37).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(2,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide · trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.45 (m, 1H), 7.26 (m, 4H), 7.06 (m, 2H), 5.12 (m, 1H), 4.57-4.35 (m, 1H), 4.05-3.63 (m, 2H), 3.41-2.87 (m, 6H), 2.68, 2.64 (2 singlets, 3H, CH_3NHC(O), rotamers), 2.28-1.74 (m, 1H), 1.65-0.77 (m, 11H); ^{13}C NMR (CD_3OD, 75 MHz, with rotamers) δ 172.2, 171.9, 171.0, 170.6, 165.4, 162.5, 162.2, 136.5, 136.3, 135.4, 135.0, 134.5, 134.1, 132.9, 132.8, 132.6, 130.6, 130.5, 128.7, 128.5, 119.9, 117.1, 116.8, 116.5, 69.0, 68.9, 55.9, 54.7, 52.3, 50.8, 42.2, 39.2, 38.0, 36.7, 33.0, 32.7, 32.5, 26.4, 20.7, 20.6, 14.6, 14.0, 13.8; MS *m/z* (ESI): 606 (M + H, 100), 608 (M + 2 + H, 70).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(2,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide · trifluoroacetate. ^{1}H NMR (CD_3OD, 300 MHz, with rotamers) δ 7.55 (m, 1H), 7.39 (m, 4H), 7.19 (m, 3H), 5.25 (m, 1H), 4.59-4.36 (m, 1H), 4.06-3.75 (m, 1H), 3.57-2.98 (m, 9H), 2.98, 2.85, 2.77 (3 singlets, 6H, CH_3NHC(O) and CH_3NHC(CH_2-CH_2)C(O), rotamers), 2.65 (m, 1H), 2.24-0.94 (m,

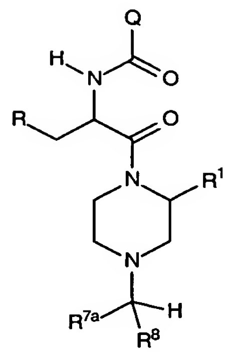
11H); ^{13}C NMR (CD_3OD, 75 MHz, with rotamers) δ 172.8, 172.6, 172.0, 171.6, 169.6, 136.8, 136.3, 134.5, 134.1, 132.8130.4, 128.5, 117.3, 116.7, 116.4, 69.2, 69.1, 63.6, 56.3, 55.0, 52.4, 52.2, 51.6, 44.1, 43.2, 39.7, 39.2, 38.0, 36.0, 33.2, 33.0, 32.8, 32.6, 26.3, 20.6, 14.7, 13.8, 13.6; MS *m/z* (ESI): 620 (M + H, 100), 622 (M + 2 + H, 70).

1-Amino-cyclopropanecarboxylic acid (1-(4-fluorobenzyl)-2-{4-[2-(2-fluorophenyl)-1-methylcarbamoyl-ethyl]-2-methyl-piperazin-1-yl}-2-oxo-ethyl)-amide · trifluoroacetate. ^1H NMR (CD_3OD, with rotamers) δ 7.27-7.03 (m, 8H), 5.07 (t, 1H, J = 7.7 Hz), 4.68-4.33 (m, 1H), 3.99 (m, 1H), 3.52 (m, 1H), 3.19-2.97 (m, 7H), 2.74-2.63 (m, 5H), 2.37-1.82 (m, 1H), 1.66 (m, 1H), 1.49-1.29 (m, 4H), 1.01 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.2, 171.8, 170.9, 165.5, 164.7, 162.2, 161.4, 134.1, 133.3, 132.8, 130.3, 125.7, 117.0, 116.8, 116.4, 65.8, 56.6, 56.4, 52.3, 51.2, 46.8, 42.0, 38.8, 38.5, 38.0, 36.7, 29.3, 26.3, 17.0, 15.9, 13.9; MS *m/z* (ESI): 528 (M + H, 100).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(3,4-difluorophenyl)-1-methyl-carbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (300MHz, CD_3OD) δ 0.880 (m, 3H), 1.177 (m, 2H), 1.393 (m, 2H), 1.444 (m, 2H), 1.493 (m, 2H), 1.651 (m, 1H), 2.631, 2.669 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 3.182 (m, 3H), 3.206 (m, 3H), 3.753 (m, 1H), 4.692 (m, 1H), 5.129 (m, 1H), 7.040 (m, 3H), 7.145 (m, 2H), 7.288 (m, 2H), ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 19.561, 20.168, 22.322, 22.663, 45.202, 46.12; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 163.3, 162.8, 162.2, 137.8, 137.1, 134.2, 134.1, 132.9, 132.7, 132.6, 127.2, 119.6, 119.4, 118.5, 118.4, 118.3, 118.2, 117.1, 116.7, 116.4, 71.114, 71.0, 56.1, 54.9, 52.3, 51.2, 50.3, 50.1, 42.9, 38.0, 36.7, 34.9, 33.1, 32.7, 26.3, 20.7, 20.6, 14.6, 13.9, 13.8; MS *m/e* 674 (M+1).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(3,4-difluorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (300MHz, CD_3OD) δ 0.902 (m, 3H), 1.091 (m, 2H), 1.481 (m, 4H), 1.655 (m, 2H), 1.753 (m, 1H),□ 2.273 (m, 1H), 2.653, 2.713 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.707 (m, 5H), 3.046 (m, 4H), 3.166 (m, 1H), 4.580 (m, 1H), 5.160 (m, 1H), 7.045 (m, 3H), 7.142 (m, 2H), 7.278 (m, 2H), ^{19}F NMR (282MHz, CD_3OD with rotamers) δ 18.901, 19.388, 21.878, 22.176, 45.099, 45.884; ^{13}C NMR (75MHz, CD_3OD with rotamers) δ 134.3, 132.8, 132.7, 127.1, 119.6, 119.4, 118.2, 117.0, 116.7, 116.4, 71.1, 56.1, 55.0, 53.8, 52.3, 51.3, 50.2, 44.0, 43.0, 39.2, 38.0, 35.0, 34.6, 33.2, 32.7, 26.2, 20.6, 14.6, 13.7; MS *m/e* 588 (M+1).

The fifth aspect of Category III comprises compounds having the formula:



wherein R is a substituted phenyl unit as described herein above and non-limiting examples of R^1, R^{7a}, R^8, and Q are defined herein below in Table XIV and in the examples which follow.

TABLE XIV

No.	R^1	Q	R^{7a}	R^8
1181	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
1182	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2-chlorophenyl)methyl
1183	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3-chlorophenyl)methyl
1184	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
1185	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2,4-dichlorophenyl)methyl
1186	$-CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1187	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1188	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1189	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1190	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1191	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1192	$-CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1193	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
1194	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2-chlorophenyl)methyl
1195	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3-chlorophenyl)methyl
1196	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
1197	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2,4-dichlorophenyl)methyl
1198	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1199	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1200	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1201	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1202	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1203	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl

1204	$-CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1205	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
1206	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2-chlorophenyl)methyl
1207	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3-chlorophenyl)methyl
1208	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
1209	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(2,4-dichlorophenyl)methyl
1210	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1211	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1212	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1213	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1214	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1215	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1216	$-CH_2CH_2CH_3$	$-CH_2OCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1217	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
1218	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	(2-chlorophenyl)methyl
1219	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	(3-chlorophenyl)methyl
1220	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
1221	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	(2,4-dichlorophenyl)methyl
1222	$-CH_3$	$-OCH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1223	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1224	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1225	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1226	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1227	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1228	$-CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1229	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	naphthylen-2-ylmethyl
1230	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	(2-chlorophenyl)methyl
1231	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	(3-chlorophenyl)methyl
1232	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	(4-chlorophenyl)methyl
1233	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	(2,4-dichlorophenyl)methyl
1234	$-CH_2CH_3$	$-OCH_3$	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1235	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1236	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1237	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1238	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1239	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl

1240	$-CH_2CH_3$	$-OCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1241	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1242	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1243	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1244	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1245	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1246	$-CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1247	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1248	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1249	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1250	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1251	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1252	$-CH_2CH_3$	$-CH(CH_3)NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1253	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1254	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1255	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1256	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1257	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1258	$-CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1259	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1260	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(2-chlorophenyl)methyl
1261	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(3-chlorophenyl)methyl
1262	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1263	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(2,4-dichlorophenyl)methyl
1264	$-CH_2CH_3$	$-C(CH_3)_2NHCH_3$	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl

The following are non-limiting examples of compounds which comprise the fifth aspect of Category III.

Preparation of 2-{3-ethyl-4-[3-(4-fluorophenyl)-2-(2-methoxy-acetylamino)-propionyl]-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propioamide HCl (0.3 g, 0.6 mmol) and methoxy acetic acid (0.05 mL, 0.6 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (0.22 g, 1.1 mmol) and 1-hydroxybenzotriazole (0.1g, 0.7 mmol) are dissolved in anhydrous DMF (2.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.2 mL, 1.7 mmol) is added. The reaction mixture is placed in a refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, the organic layer is separated, and the aqueous layer is extracted

with EtOAc (3x30 mL). The organic extracts are combined, washed with water (2x50 mL), dried over Na_2SO_4 and concentrated *in vacuo* and the resulting crude product is purified by preparative HPLC to afford 0.18 g (44% yield) of the trifluoroacetate salt of the desired product. ^1H NMR (CD_3OD, δ): 7.88 – 7.68 (m, 4H), 7.49 – 7.00 (m, 7H), 5.25 – 5.12 (m, 1H), 4.98 – 4.92 (m, 4H), 4.70 (br s, 0.5H), 4.52 (d, J = 13.0 Hz, 0.5 H), 4.18 (d, J = 10.4 Hz, 0.5H), 3.96 (dd, J = 13.0, 6.5 Hz, 0.5H), 3.86 (s, 2H), 3.75 (t, J = 3.9 Hz, 0.5H), 3.61 (d, J = 13.0 Hz, 0.5H), 3.52 – 3.18 (m, 7H), 3.18 – 2.92 (m, 3H), 2.85 – 2.78 (m, 0.5H), 2.60 – 2.45 (m, 2H), 2.12 – 2.05 (m, 0.5H), 1.98 – 1.70 (m, 2H), 0.85 – 0.78 (m, 3H); ^{13}C NMR, δ 173.0, 172.0, 170.0, 168.0, 166.0, 163.0, 162.0, 135.5, 134.4, 134.1, 133.0, 132.8, 132.7, 129.9, 129.7, 129.6, 129.1, 129.0, 128.6, 127.8, 127.5, 127.3, 117.0, 116.8, 116.5, 72.7, 71.4, 71.0, 60.0, 56.0, 53.4, 51.5, 51.4, 51.1, 51.0, 40.5, 39.9, 38.4, 35.4, 35.3, 26.5, 24.1, 23.4, 11.0, 10.8. HRFAB(positive) m/e 563.3034 calculated for $C_{32}H_{39}FN_4O_4$ $(M+H)^+$, Found 563.3051.

Preparation of [2-[2-ethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester trifluoroacetate: To a cold solution of 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-ethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propioamide HCl, **41**, (0.3g, 0.6 mmol) in anhydrous DCM (5 mL) is added methyl chloroformate (0.1 mL, 1.3 mmol) and DIEA (0.2 mL, 1.1 mmol). The reaction mixture is allowed to stir for 2 hours at this temperature. EtOAc (15 mL) and water (15 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 20 mL). All organic layers are combined and washed with water (2 x 20 mL), and dried over Na_2SO_4. Solvent is removed *in vacuo* and the product is purified by preparative HPLC to give TFA salt (0.14 g, 0.21 mmol, 35% yield). A small amount of product was converted into the free base by treating with $NaHCO_3$ to obtain NMR spectra. ^1H NMR ($CDCl_3$, δ): 7.83 –7.75 (m, 3H), 7.67 (s, 1H), 7.46 – 7.28 (m, 3H), 7.17 – 7.13 (m, 2H), 7.00 – 6.94 (m, 2H), 6.60 – 6.40 (m, 0.5H), 5.66 – 5.63 (m, 0.5H), 4.95 – 4.78 (m, 1H), 4.30 (br s, 0.5H), 4.32 – 4.28 (m, 0.5H), 3.68 (s, 2H), 3.61 (s, 1H), 3.50 – 3.28 (m, 3H), 3.00 – 2.76 (m, 8H), 2.55 – 2.40 (m, 2H), 2.19 (td, J = 10.4, 2.6 Hz, 1H), 1.90 – 1.75 (m, 1H), 1.65 – 1.22 (m, 2H), 0.83 (quartet, J = 7.2 Hz, 3H); ^{13}C NMR; δ 171.9, 170.3, 169.8, 163.8, 160.5, 156.4, 137.3, 133.7, 132.3, 132.1, 132.0, 131.4, 131.3, 131.2, 128.3, 127.9, 127.8, 127.7, 126.3, 125.7, 115.9, 115.7, 115.4, 70.7, 70.5, 55.4, 52.5, 51.9, 51.7, 51.6, 51.1, 51.0, 50.2, 49.7, 41.8, 40.0, 39.2, 37.9, 32.3, 26.2, 26.0, 23.3, 22.2, 10.8, 10.4. HRFAB (positive) m/e 549.2877 calculated for $C_{31}H_{37}FN_4O_4$ $(M+H)^+$, Found 549.2868.

3-(3,4-Dichlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-(2-methyl-2-methylamino-propionyl amino)-propionyl}-3-methyl-piperazin-1-yl}-N-methyl-propionamide trifluoroacetate: ^1H NMR (CD_3OD, δ): 7.20 – 7.16 (m, 2H), 7.04 (br s, 2H), 6.91 – (m, 3H), 4.85 (br s, 1H), 4.04 (d J = 13.2 Hz, 0.5H), 3.76 – 3.55 (m, 1H), 3.12 – 3.07 (m, 7H), 2.81 – 2.58 (m,

6H), 2.44 – 2.30 (m, 6H), 1.58 – 1.55 (m, 0.5H), 1.33 – 1.22 (m, 6H), 1.08 – 0.95 (m, 2H), 0.85 – 0.83 (m, 1H). HRFAB(positive) m/e 594.241399 calculated for $C_{29}H_{38}Cl_2FN_5O_3$ $(M+H)^+$, Found 594.238873.

3-(3,4-Dichlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-(2-methylamino-propionylamino)-propionyl]-3-methyl-piperazin-1-yl}-N-methyl-propionamide: ^1H NMR (CD_3OD): δ 7.59 – 7.54 9m, 2H), 7.44 (bs, 2H), 7.30 – 7.19 (m, 3H), 5.28 – 5.19 (m, 1H), 4.44 (d, J = 12.4 Hz, 0.5H), 4.14 – 3.95 (m, 2H), 3.61 – 3.60 (m, 0.5H), 3.48 – 3.46 (m, 3H), 3.32 – 2.92 (m, 7H), 2.82 – 2.78 (m, 4H), 2.72 – 2.67 (m, 5H), 1.97 – 1.87 (m, 0.5H), 1.64 (d, J = 7.0 Hz, 3H), 1.47 – 1.34 (m, 1.5H), 1.24 – 1.22 (m, 1H); ^{13}C NMR (CD_3OD): δ 173.0, 172.0, 170.0, 165.5, 162.3, 140.3, 139.8, 133.9, 133.5, 132.9, 131.8, 130.8, 116.8, 70.8, 58.6, 56.4, 51.8, 51.2, 50.3, 50.0, 49.6, 46.8, 42.0, 39.2, 38.5, 34.6, 32.2, 26.3, 17.2, 16.7, 16.0. HRFAB(positive) m/e 580.225749calculated for $C_{28}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 580.223868.

3-(3,4-Dichlorophenyl)-2-{4-[2-(2-dimethylamino-acetylamino)-3-(4-fluorophenyl)-propionyl]-3-methyl-piperazin-1-yl}-N-methyl-propionamide. ^1H NMR (CD_3OD): δ 7.68 – 7.60 (m, 2H), 7.55 – 7.45 (m, 2H), 7.38 – 7.18 (m, 3H), 5.39 – 5.30 (m, 1H), 4.98 – 4.91 (m, 0.5H), 4.58 – 4.49 (m, 0.5H), 4.20 – 4.10 (m, 3H), 3.72 – 3.48 (m, 5H), 3.32 – 3.08 (m, 10H), 2.92 – 2.85 (m, 5H), 2.58 – 2.48 (m, 0.5H), 2.05 –1.92 (m, 0.5H), 1.54 – 1.48 (m, 1.5H), 1.30 – 1.20 (m, 1.5H); ^{13}C NMR δ 174.0, 172.0, 165.5, 162.7, 140.3, 139.9, 133.8, 133.5, 132.8, 131.8, 130.7, 117.1, 116.8, 116.5, 70.9, 70.7, 59.4, 56.6, 56.4, 52.0, 51.2, 50.2, 50.0, 49.6, 49.4, 49.1, 46.844.8, 42.0, 39.3, 38.5, 34.9, 34.7, 26.3, 17.1, 16.0. HRFAB(positive) m/e 580.225749 calculated for $C_{28}H_{36}Cl_2FN_5O_3$ $(M+H)^+$, Found 580.223768.

2-{4-[3-(4-Fluorophenyl)-2-methylamino-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-3-naphthalen-2-yl-N-(2,2,2-trifluoroethyl)-propionamide: ^1H NMR (300 MHz, MeOD, Rotamers) δ 8.78-8.84 (m, 0.4H), 7.78-7.91 (m, 3H), 7.72 (s, 0.2H), 7.65 (s, 0.8H), 7.38-7.59 (m, 3H), 7.13-7.30 (m, 2H), 6.94-7.11 (m, 2H), 5.58-5.72 (m, 1H), 4.52-4.66 (m, 1.6H), 3.82-4.36 (m, 2H), 3.40-3.66 (m, 2H), 3.14-3.32 (m, 3.4H), 2.78-3.03 (m, 1.4H), 2.65-2.74 (m, 0.6H), 2.61 (s, 0.6H), 2.58 (s, 2.4H), 0.64-1.16 (m, 2H), 0.18-0.58 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.83, 170.14, 168.35, 167.42, 165.92, 162.82, 162.66, 162.35, 135.67, 135.28, 134.39, 133.1, 133.05, 132.58, 132.46, 130.91, 130.39, 129.76, 129.16, 129.09, 128.90, 128.49, 128.07, 127.86, 127.35, 117.83, 117.54, 117.36, 117.08, 60.63, 60.70, 59.42, 58.46, 58.14, 57.32, 43.90, 43.13, 42.85, 42.36, 41.90, 41.44, 40.98, 40.96, 39.63, 37.38, 36.84, 35.92, 35.75, 32.58, 20.03, 19.88, 14.09; MS (ESMS) *m/z* 601.3 $(M+H)^+$.

[2-{4-[2-(3,4-Dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester: ^{1}H NMR (300 MHz, MeOD, Rotamers) δ 7.40-7.50 (m, 2H), 7.23-7.34 (m, 2H), 7.12-7.21 (m,1H), 6.99-7.21 (m, 2H), 4.78-4.88 (m, 1H), 4.57-4.68 (m, 0.6H), 4.28-4.37 (m, 0.4H), 4.00-4.10 (m, 0.4H), 3.64 (s, 3H), 3.44-3.54 (m, 0.4H), 2.62-3.32 (m,12H), 2.12-2.28 (m, 0.4H), 1.26-1.77 (m, 2.5H), 0.94-1.26 (m, 1.5H), 0.88 (dd, J = 13.2, 6.6 Hz, 3H); MS (ESMS) *m/z* 581.4, 583.2, 585.6 $(M+H)^+$, Cl_2 isotope pattern.

[2-{4-[2-(2-Chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.20 (m, 1H), 7.07 (m, 5H), 6.85 (m, 2H), 4.62 (m, 1H), 4.47-4.16 (m, 1H), 3.89-3.49 (m, 1H), 3.42 (s, 3H), 3.25-2.64 (m, 9H), 2.45, 2.40 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.10-1.60 (m, 1H), 1.42-1.23 (m, 2H), 0.90-0.66 (m, 5H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.7, 172.5, 172.0, 170.3, 165.4, 162.2, 159.3, 137.0, 135.6, 134.2, 133.5, 132.8, 132.7, 131.1, 130.9, 130.4, 129.9, 128.6, 128.4, 117.0, 116.4, 69.7, 69.3, 55.6, 54.0, 53.7, 53.4, 53.1, 51.5, 41.4, 40.2, 38.8, 33.2, 32.5, 26.4, 20.6, 20.5, 14.6; MS *m/z* (ESI): 547 (M + H, 100), 549 (M + 2 + H, 35).

[2-{4-[2-(4-Chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester trifluoroacetate. ^{1}H NMR (CD_3OD, with rotamers) δ 7.45 (m, 4H), 7.20 (m, 2H), 7.05 (m, 2H), 4.84 (m, 1H), 4.72-4.03 (m, 1H), 4.16-3.76 (m, 1H), 3.70 (s, 3H), 3.43 (m, 1H), 3.24-2.97 (m, 8H), 2.66, 2.61 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.50-1.89 (m, 1H), 1.75-0.99 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.6, 172.3, 170.9, 169.3, 164.4, 162.8, 161.6, 161.4, 159.1, 158.7, 137.3, 135.9, 134.4, 134.1, 134.0, 132.7, 132.5, 132.2, 132.1, 130.0, 129.7, 118.4, 116.7, 116.5, 116.4, 116.3, 71.3, 70.8, 55.0, 53.9, 53.4, 53.2, 53.1, 52.9, 51.2, 49.9, 40.7, 39.8, 38.4, 38.0, 34.3, 33.0, 32.3, 26.2, 26.1, 20.4, 20.2, 14.3, 14.2; MS *m/z* (ESI): 547 (M + H, 100), 549 (M + 2 + H, 35).

[2-{4-[2-(3-Chlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.27 (m, 5H), 7.18 (m, 1H), 7.05 (m, 2H), 4.84 (m, 1H), 4.68-4.39 (m, 1H), 4.13-3.70 (m, 1H), 3.63 (s, 3H), 3.38-2.89 (m, 9H), 2.66, 2.61 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.37-1.81 (m, 1H), 1.69 (m, 1H), 1.47 (m, 1H), 1.11 (m, 2H), 0.90 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.0, 172.8, 172.0, 170.4, 165.4, 162.2, 159.3, 141.7, 140.3, 135.8, 135.6, 134.3, 132.9, 132.8, 132.7, 131.5, 131.3, 130.9, 129.3, 128.7, 128.2, 117.0, 116.7, 116.4, 71.5, 71.0, 55.5, 54.2, 53.8, 53.3, 53.1, 51.3, 41.3, 40.1, 38.7, 34.9, 33.2, 32.5, 26.4, 20.6, 20.5, 14.5; MS *m/z* (ESI): 547 (M + H, 100), 549 (M + 2 + H, 35).

3-(4-Chlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-(2-hydroxy-2-methyl-propionylamino)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.18-7.09 (m, 6H), 6.94 (m, 2H), 4.97 (m, 1H), 4.59-4.29 (m, 1H), 3.99-3.66 (m, 1H), 3.53-3.28 (m, 1H), 3.15-2.75 (m, 8H), 2.54, 2.49 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.30-1.72 (m, 1H), 1.55-1.42 (m, 2H), 1.22, 1.16 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.01 (m, 2H), 0.80 (t, 3H, J = 7.2 Hz); ^{13}C NMR (CD_3OD, with rotamers) δ 179.3, 178.9, 171.9, 171.8, 171.3, 169.8, 164.4, 162.8, 161.4, 161.2, 137.6, 136.3, 134.3, 133.8, 133.7, 132.8, 132.7, 132.6, 132.2, 132.1, 129.9, 129.7, 118.4, 116.7, 116.6, 116.4, 116.3, 73.8, 71.3, 70.9, 55.2, 54.2, 53.9, 51.2, 51.0, 50.8, 50.0, 40.9, 40.2, 38.6, 38.3, 34.6, 34.4, 33.2, 32.4, 28.0, 27.9, 27.8, 26.2, 26.1, 20.3, 20.2, 14.4, 14.3; MS *m/z* (ESI): 575 (M + H, 100), 577 (M + 2 + H, 30).

3-(3-Chlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-(2-hydroxy-2-methyl-propionylamino)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.17 (m, 5H), 7.07-6.89 (m, 3H), 4.98 (m, 1H), 4.59-4.30 (m, 1H), 4.00-3.66 (m, 1H), 3.54-3.27 (m, 1H), 3.13-2.75 (m, 8H), 2.54, 2.49 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.31-1.71 (m, 1H), 1.61-1.39 (m, 2H), 1.22, 1.16 (2 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.02 (m, 2H), 0.80 (m 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 179.5, 179.1, 172.2, 172.0, 171.5, 170.0, 165.5, 162.2, 161.6, 161.1, 141.5, 140.1, 135.8, 135.6, 133.9, 132.9, 132.8, 131.5, 131.3, 129.3, 129.2, 128.7, 117.1, 116.7, 116.4, 74.0, 71.5, 71.0, 55.5, 54.5, 54.2, 51.5, 51.2, 51.1, 41.2, 40.5, 38.8, 38.5, 35.0, 34.9, 33.4, 32.6, 28.2, 28.1, 26.4, 20.5, 20.4, 14.5; MS *m/z* (ESI): 575 (M + H, 100), 577 (M + 2 + H, 30).

3-(2,4-Dichlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-(2-hydroxy-2-methyl-propionyl-amino)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-propionamide trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.46 (d, 1H, J = 8.8 Hz), 7.24 (m, 4H), 7.04 (dd, 2H, J = 18.2, 8.9 Hz), 5.05 (m, 1H), 4.59-4.30 (m, 1H), 3.93-3.66 (m, 1H), 3.54-3.35 (m, 1H), 3.18-2.94 (m, 6H), 2.77 (m, 2H), 2.67, 2.62 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.15-1.69 (m, 1H), 1.58-1.41 (m, 2H), 1.31, 1.28, 1.25 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers), 1.10 (m, 2H), 0.86 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 179.0, 178.8, 172.2, 172.0, 171.5, 165.5, 162.2, 136.5, 136.4, 135.5, 135.0, 134.6, 134.0, 133.0, 130.6, 130.5, 128.7, 128.5, 117.0, 116.7, 116.4, 74.1, 69.4, 69.0, 56.0, 54.7, 54.2, 51.4, 51.0, 50.9, 42.0, 40.5, 39.1, 39.0, 33.5, 32.8, 32.7, 32.6, 28.3, 28.1, 26.4, 20.6, 20.4, 14.6; MS *m/z* (ESI): 609 (M + H, 100), 611 (M + 2 + H, 70).

{1-(4-Fluorobenzyl)-2-[4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-2-propyl-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid methyl ester. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00~7.90 (m, 11H), 4.84 (m, 1H), 3.80~4.20 (m, 1H), 3.99~3.90 (m, 14H), 2.66 (m, 3H), 1.50~1.80 (m, 2H), 1.00~1.40 (m, 2H), 0.93 (m, 3H); MS (ES-MS) m/z 563 (M+1).

2-{4-[3-(4-Fluorophenyl)-2-(2-hydroxy-2-methyl-propionylamino)-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93~7.90 (m, 11H), 5.00~5.18 (m, 1H), 3.20~3.70 (m, 4H), 2.70~3.01(m, 9H), 1.00~1.70 (m, 10H), 0.88 (m, 3H); MS (ES-MS) *m/z* 591 (M+1).

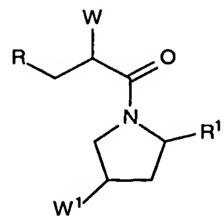
2-{4-[3-(4-Chlorophenyl)-2-methylamino-propionyl]-3-propyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.000~7.83 (m, 11H), 3.20~3.70 (m, 4H), 2.40~3.10 (m, 10H), 2.05~2.35 (m, 5H), 1.00~1.83 (m, 4H), 0.91 (m, 3H); MS (ES-MS) *m/z* 535 (M+1).

[2-{4-[2-(2,4-Dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-propyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid methyl ester trifluoroacetate: ^{1}H NMR (CD_3OD, with rotamers) δ 7.47 (d, 1H, J = 8.7 Hz), 7.26 (m, 4H), 7.04 (dd, 2H, J = 16.4, 8.1 Hz), 4.81 (m, 1H), 4.61-4.33 (m, 1H), 4.04-3.56 (m, 1H), 3.62 (s, 3H), 3.38 (m, 1H), 3.20-2.77 (m, 8H), 2.68, 2.64 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.19-1.72 (m, 1H), 1.57-1.39 (m, 2H), 1.03 (m, 2H), 0.86 (m, 3H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.3, 173.0, 171.0, 165.4, 162.2, 159.3, 158.9, 136.4, 135.2, 134.6, 134.3, 133.0, 132.8, 132.7, 130.6, 130.5, 128.7, 128.5, 116.9, 116.7, 116.4, 69.4, 69.1, 55.8, 54.2, 53.9, 53.4, 53.1, 51.2, 50.6, 41.8, 40.2, 39.1, 38.8, 33.2, 32.7, 32.5, 26.4, 20.5, 14.6; MS *m/z* (ESI): 581 (M + H, 100), 583 (M + 2 + H, 70)

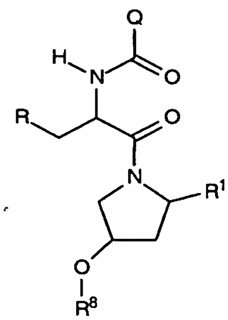
2-{4-[3-(4-Fluorophenyl)-2-(2-methylamino-acetylamino)-propionyl]-3-methyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide: ^{1}H NMR (300 MHz, CD_3OD, Rotamers) δ 7.75-7.89 (m, 3H), 7.69 (s, 1H), 7.22-7.54 (m, 5H), 6.99-7.15 (m, 2H), 5.03-5.22 (m, 1H), 4.34-4.49 (m, 0.6H), 3.42-4.12 (m, 6H), 2.48-3.30 (m, 9H), 1.85-2.00 (m, 1H), 1.02-1.43 (m, 3H); MS (ESMS) *m/z* 548.4 $(M+H)^+$.

The compounds which comprise Category III are also compounds wherein R^{7a} is hydrogen, as described herein above, and as provided by example in the description of Category II analogs according to the present invention.

The Category IV melanocortin receptor ligands according to the present invention comprises the 2-hydrocarbyl-pyrrolidines having the general scaffold with the formula:



the first aspect of which comprises pyrrolidine analogs having the formula:



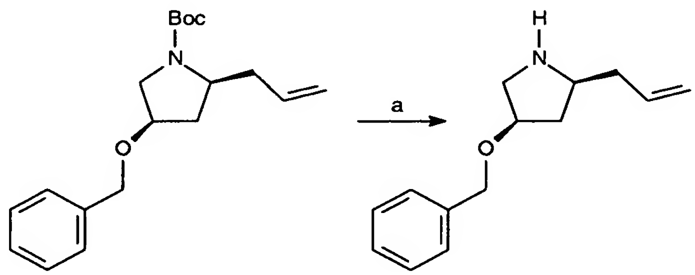
wherein R, R^1, and R^8 are defined herein above. The compounds which comprise the first aspect of Category IV can be prepared by the procedure outline herein below in Scheme XVI. Starting material **51** can be obtained from N-Boc-3-(*R*)-hydroxypyrrolidine as set forth therein below.

Preparation of *N*-Boc-3-*R*-hydroxypyrrolidine: Di-*tert*-butyl dicarbonate (14.0 g, 63.1 mmol) is added to a stirred solution of 3-*R*-hydroxypyrrolidine (5.0 g, 57.4 mol) and triethylamine (16 mL, 114.8 mmol) dissolved in dichloromethane (58 ml) at 0 °C. The resulting solution is allowed to warm to room temperature and stirred for 4 hours. The solution is then diluted with dichloromethane (50 mL), washed twice with 1 N HCl and twice with aq. $NaHCO_3$ solution. The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product (9.9 g, 92 %) as a white solid which is sufficiently pure for use without further purification.

Preparation of *N*-Boc-2-*S*-allyl-4-*R*-hydroxypyrrolidine: A solution of *N*-Boc-3-*R*-hydroxypyrrolidine (3.0 g, 16.0 mmol), and TMEDA (6.4 mL, 40.1mmol) is dissolved in THF (50 mL) and cooled to –78 °C. To this reaction mixture is added a solution of 1.3 M *sec*-butyl lithium (50 mL) in cyclohexanes with stirring. The resulting orange-colored mixture is allowed to warm to -40 °C and stirred for 2.75 hours. The mixture is again cooled to –78 °C and allyl bromide (3.1 mL, 35.3 mmol) is added. This mixture is slowly warmed to room temperature with stirring over 4.5 hours. The reaction is quenched with aq. NH_4Cl solution and extracted with ethyl acetate (150 mL). The organic layer is then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The oily residue is purified over silica gel (CH_2Cl_2/acetone, 3:1) to afford the desired product (2.0 g, 56%) as a clear oil.

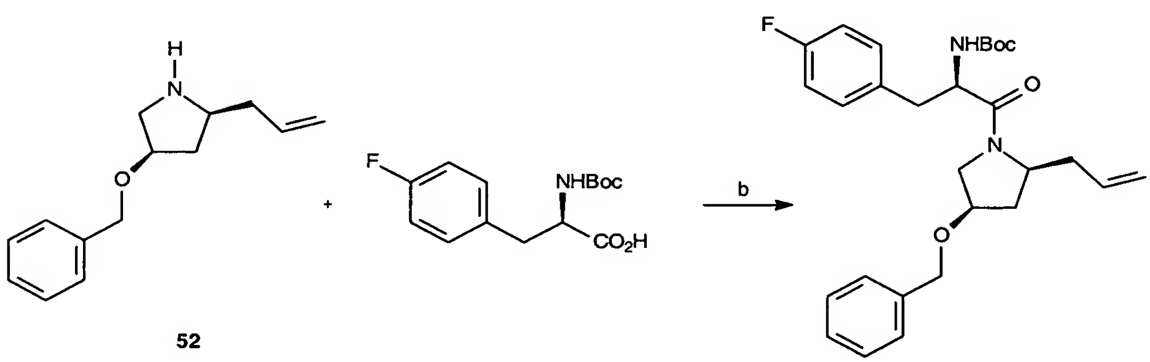
Preparation of *N*-Boc-2-(*S*)-allyl-4-(*R*)-(benzyloxy)pyrrolidine: Sodium hydride (408 mg, 11.5 mmol) is added in portions to a stirred solution of *N*-Boc-2-*S*-allyl-4-*R*-hydroxypyrrolidine (2.0 g, 8.8 mmol) in DMF at 0 °C and the reaction mixture is stirred for 20 min. Benzylbromide (2.3 g, 13.2 mmol) in DMF(5 mL) is then added and the resulting solution is stirred for 5 hours at room temperature. The reaction is quenched with aq. NH_4Cl solution and extracted twice with ethyl acetate. The combined organic layers are dried over Na_2SO_4, filtered and concentrated *in vacuo* to a yellow oil. The oil residue is purified over silica gel (hexanes/EtOAc, 6:1) to afford the desired product as a clear oil.

Scheme XVI



51 52

Reagents and conditions: (a) TFA, CH_2Cl_2; rt 1hr.



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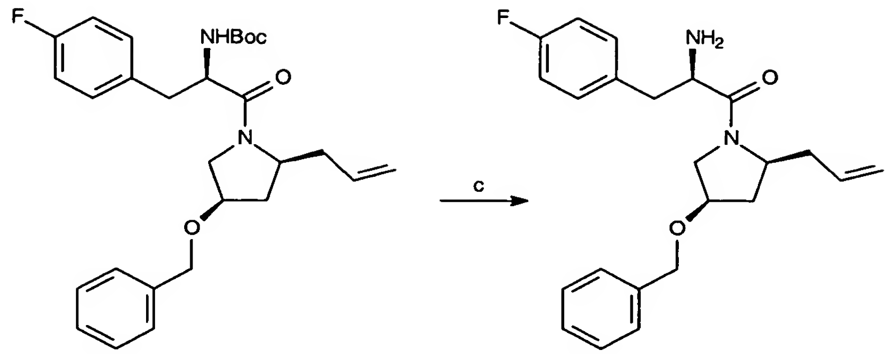
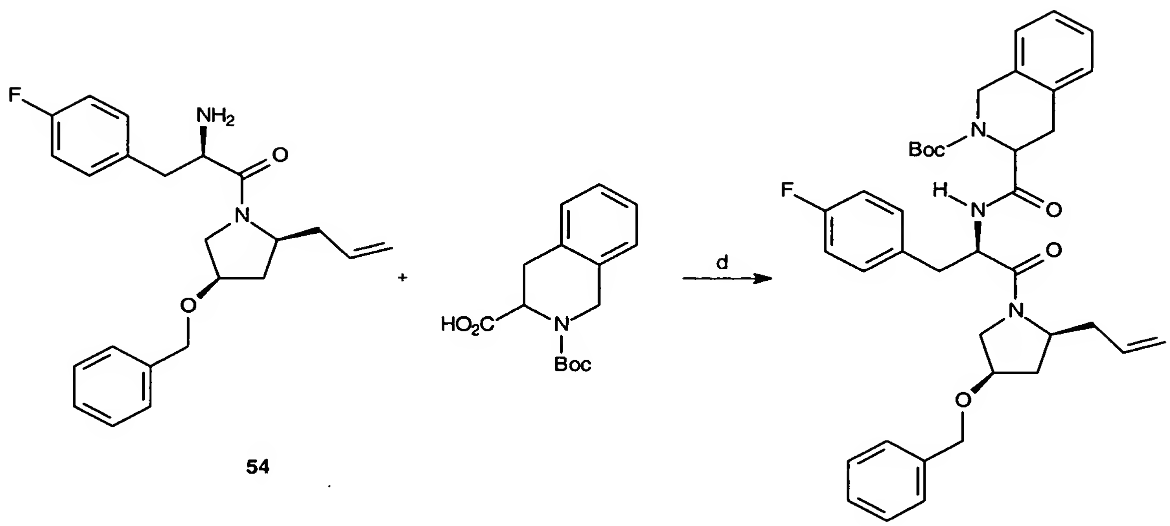
Reagents and conditions: (b) EDCI, HOBt, NMM, DMF; 0 °C, 2.5 hr.



53 54

Reagents and conditions: (c) TFA, CH_2Cl_2; rt, 1hr.



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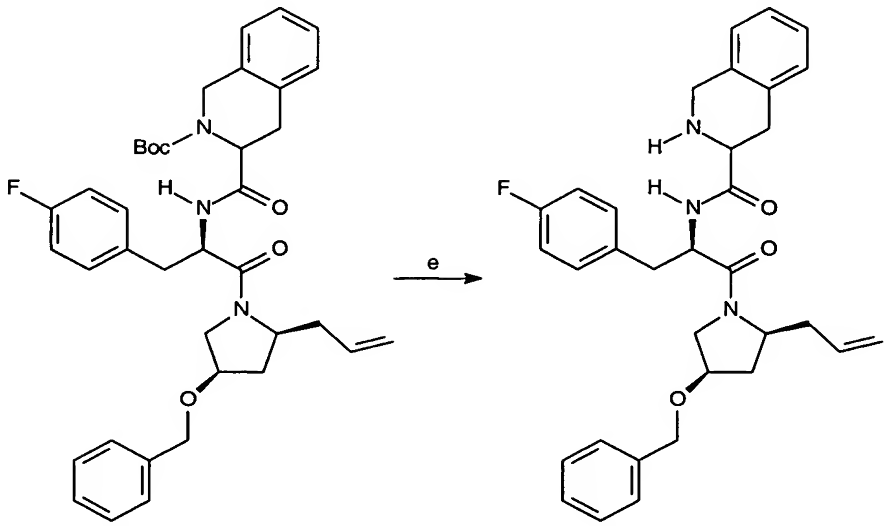
Reagents and conditions: (d) EDCI, HOBt, NMM, DMF; 0 °C, 2.5 hr..



55 56

Reagents and conditions: (e) TFA, CH_2Cl_2; rt, 1hr.

EXAMPLE 16

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid [2-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluor-benzyl)-2-oxo-ethyl]-amide (56)

Preparation of 2-allyl-4-benzyloxy-pyrrolidine (52): 2-Allyl-4-benzyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester, **51**, (0.76g, 2.4 mmol) is dissolved in methylene chloride (33 mL), and trifluoroacetic acid (25 mL) is added. The reaction mixture is stirred for 1hour and then concentrated *in vacuo.* MeOH (40 mL) is added and the solvent is removed *in vacuo* to afford the desired product in approximately quanitative yield as a viscous oil which is used without further purification.

Preparation of [2-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester (53): To a solution of 2-allyl-4-benzyloxy-pyrrolidine, **52**, (0.52 g. 2.4 mmol) in DMF (15 mL) are added Boc-D-(4-fluorophenyl)alanine (0.74g, 2.6 mmol), 1-hydroxybenzotriazole hydrate (0.73 g, 4.8 mmol), and N-methylmorpholine (1.5 g, 14.4 mmol), EDC (0.55 g, 2.9 mmol) at 0 °C. The reaction mixture is stirred at 0°C for 1hr and then warmed to room temp and stirred an additional 1.5hr. The reaction is quenched with saturated NH_4Cl solution and the mixture is extracted 3 times with EtOAc (70 mL). The organic layers are combined, washed with saturated NaCl solution, dried over Na_2SO_4, and the solvent is removed in vacuo. The crude product is purified over silica (88/12 hexane/ethyl acetate) to afford 0.67 g (58% yield) of the desired compound as a white solid. ^1H NMR (300 MHz, MeOD, Rotamers) δ 7.20-7.50 (m, 6.6H), 6.52-7.10 (m, 2.4H), 5.58-5.85 (m, 1H), 4.85-5.20 (m, 2H), 4.30-4.61 (m,

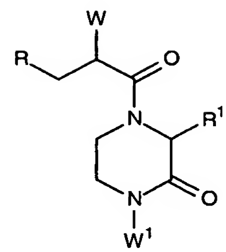
3H), 3.11-4.25 (m, 5H), 2.85-3.05 (m, 2H), 2.47-2.80 (m, 1H), 1.83-2.27 (m, 2H), 1.33-1.48 (m, 9H); MS (ESMS) *m/z* 483.1 $(M+H)^+$.

Preparation of 1-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-2-amino-3-(4-fluorophenyl)-propan-1-one (54): [2-(2-Allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluorobenzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester, **53**, (0.67g, 1.4 mmol) is dissolved in methylene chloride (21 mL), and trifluoroacetic acid (9 mL) is added. The reaction mixture is stirred for 1hourr and then concentrated *in vacuo*. MeOH (40 mL) is added and the solvent is removed *in vacuo* to afford the desired product in approximately quanitative yield as a viscous oil which is used without further purification.

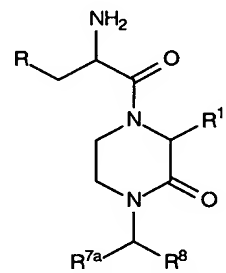
Preparation of 3-[2-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (55): To solution of 1-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-2-amino-3-(4-fluorophenyl)-propan-1-one, **54,** (1.4 mmol) is dissolved in DMF (10 mL) are added N-Boc-tetrahydroisoquinoline-3-carboxylic acid (0.47g, 1.5 mmol), 1-hydroxybenzotriazole (0.43g, 2.8 mmol), N-methylmorpholine (0.84g, 8.3 mmol) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (0.32g, 1.7 mmol) at 0 °C. The reaction mixture is stirred at 0°C for 1hour and then warmed to room temperature and stirred an additional 1.5 hour. The reaction is quenched with saturated NH_4Cl solution and then extracted 3 times with EtOAc (70 mL). The organic layers are combined, washed with saturated NaCl solution, dried over Na_2SO_4, and the solvent is removed *in vacuo*. The crude product is purified over silica to afford 0.69 g (77%yield) of the desired product as a white solid. ^1H NMR (300 MHz, MeOD, Rotamers) δ 6.90-7.41 (m, 13H), 5.55-5.81 (m, 1H), 4.32-5.12 (m, 8H), 3.94-4.18 (m, 2H), 2.75-3.89 (m, 6H), 2.39-2.64 (m, 1H), 1.78-2.29 (m, 2H), 1.20-1.64 (m, 10H); MS (ESMS) *m/z* 642.2 $(M+H)^+$.

Preparation of 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid [2-(2-allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluor-benzyl)-2-oxo-ethyl]-amide (56): 3-[2-(2-Allyl-4-benzyloxy-pyrrolidin-1-yl)-1-(4-fluorobenzyl)-2-oxo-ethylcarbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, **55**, (200 mg) is dissolved into CH_2Cl_2 (3 mL) and trifluoroacetic acid (1 mL) is added. The reaction mixture is stirred for 5 hours and concentrated. The residue is purified by reverse phase HPLC to afford 50 mg of the desired product. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80~7.50 (m, 13H), 5.75 (m, 1H), 5.06 (m, 2H), 4.30~4.70 (m, 6H), 4.06 (m, 2H), 3.75 (m, 1H), 2.90~3.30 (m, 6H), 2.69 (m, 1H), 2.23 (m, 1H), 1.80~2.00 (m, 2H); MS (ES-MS) m/z 542 (M+1).

Category V melanocortin receptor ligands according to the present invention comprise the 2-oxo-3-hydrocarbyl-piperazines having the general scaffold with the formula:



wherein R^1 comprises a substituted alkyl unit. The first aspect of Category V comprises the 2-oxo-3-hydrocarbyl-piperazines having the formula:



wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{7a} and R^8 are provided herein below in Table XV.

TABLE XV

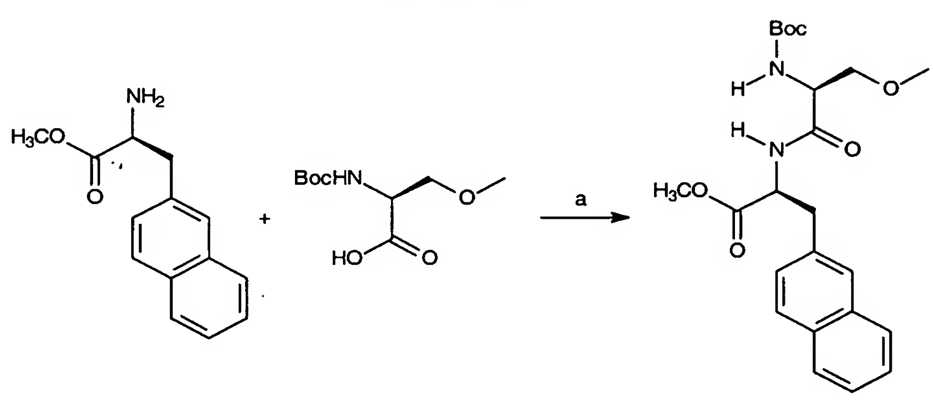
No.	R^1	R^{7a}	R^8
1265	methoxymethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1266	methoxyethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1267	methoxypropyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1268	ethoxymethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1269	ethoxyethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1270	ethoxypropyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1271	propoxymethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1272	propoxyethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1273	propoxypropyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1274	*iso*-propoxymethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1275	*iso*-propoxyethyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1276	*iso*-propoxypropyl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1277	methoxymethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1278	methoxyethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1279	methoxypropyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1280	ethoxymethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl

1281	ethoxyethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1282	ethoxypropyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1283	propoxymethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1284	propoxyethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1285	propoxypropyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1286	*iso*-propoxymethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1287	*iso*-propoxyethyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1288	*iso*-propoxypropyl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
129	methoxymethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1290	methoxyethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1291	methoxypropyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1292	ethoxymethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1293	ethoxyethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1294	ethoxypropyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1295	propoxymethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1296	propoxyethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1297	propoxypropyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1298	*iso*-propoxymethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1299	*iso*-propoxyethyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1300	*iso*-propoxypropyl	-C(O)NHCH$_3$	(2,4-dichlorophenyl)methyl
1301	methoxymethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1302	methoxyethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1303	methoxypropyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1304	ethoxymethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1305	ethoxyethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1306	ethoxypropyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1307	propoxymethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1308	propoxyethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1309	propoxypropyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1310	*iso*-propoxymethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1311	*iso*-propoxyethyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1312	*iso*-propoxypropyl	-C(O)NH$_2$	naphthylen-2-ylmethyl
1313	methoxymethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1314	methoxyethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1315	methoxypropyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1316	ethoxymethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl

1317	ethoxyethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1318	ethoxypropyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1319	propoxymethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1320	propoxyethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1321	propoxypropyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1322	*iso*-propoxymethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1323	*iso*-propoxyethyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1324	*iso*-propoxypropyl	-C(O)NH$_2$	(4-chlorophenyl)methyl
1325	methoxymethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1326	methoxyethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1327	methoxypropyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1328	ethoxymethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1329	ethoxyethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1330	ethoxypropyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1331	propoxymethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1332	propoxyethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1333	propoxypropyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1334	*iso*-propoxymethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1335	*iso*-propoxyethyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl
1336	*iso*-propoxypropyl	-C(O)NH$_2$	(2,4-dichlorophenyl)methyl

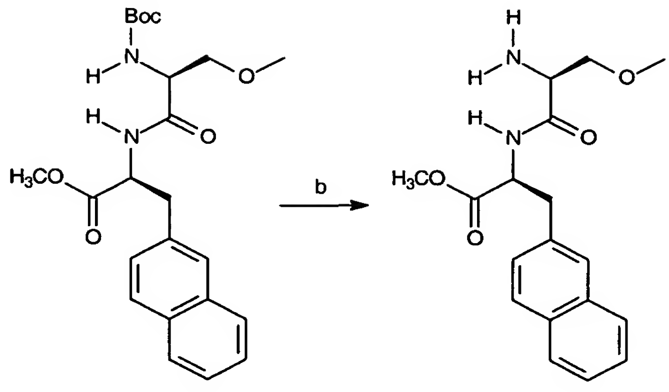
The compounds of the first aspect of Category V can be suitably prepared by the procedure outlined herein below in Scheme XVII.

Scheme XVII



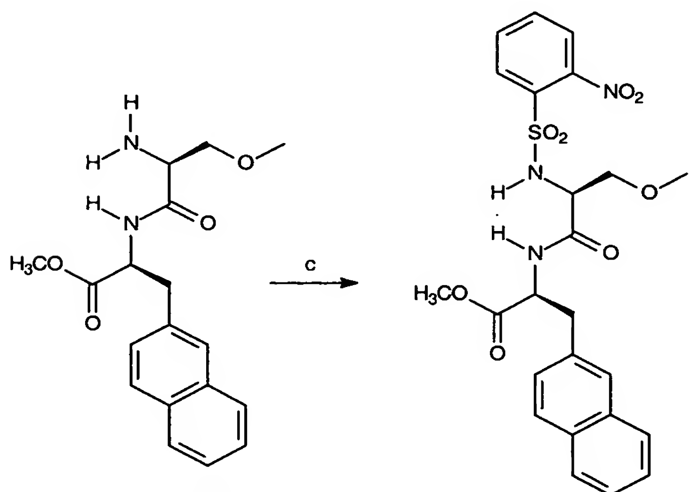
57

Reagents and conditions: (a) EDCI, HOBt, NMM, DMF; 0 °C, 18 hr.



57 **58**

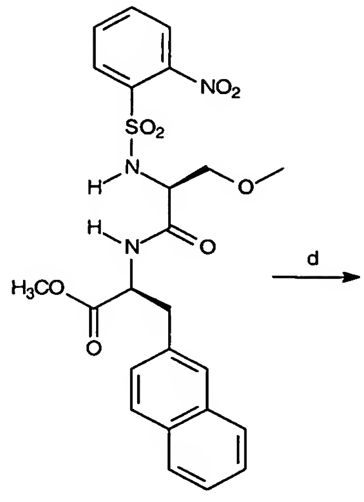
Reagents and conditions: (b) 4N HCl, dioxane; rt, 1 hr.



58

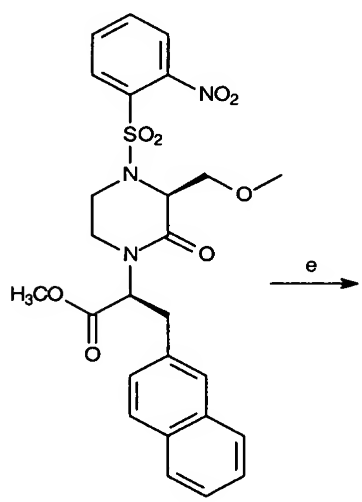
59

Reagents and conditions: (c) o-NBS, THF; 0 °C to rt, 15 hr.



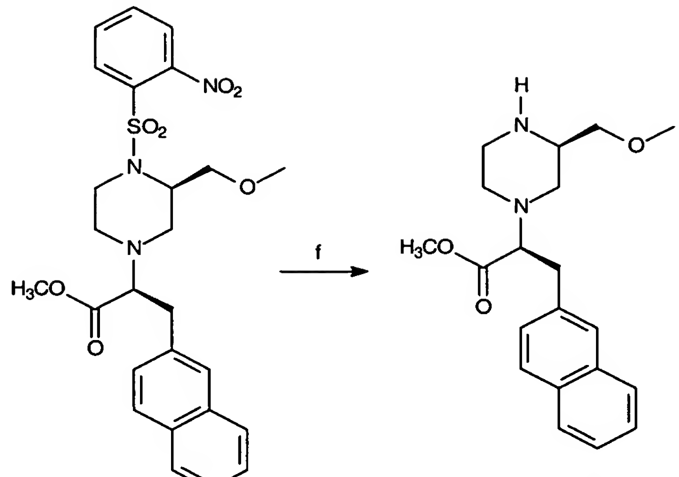
59 **60**

Reagents and conditions: (d) 1,2-dibromoethane, DMF; 60 °C, 18 hr.



60 **61**

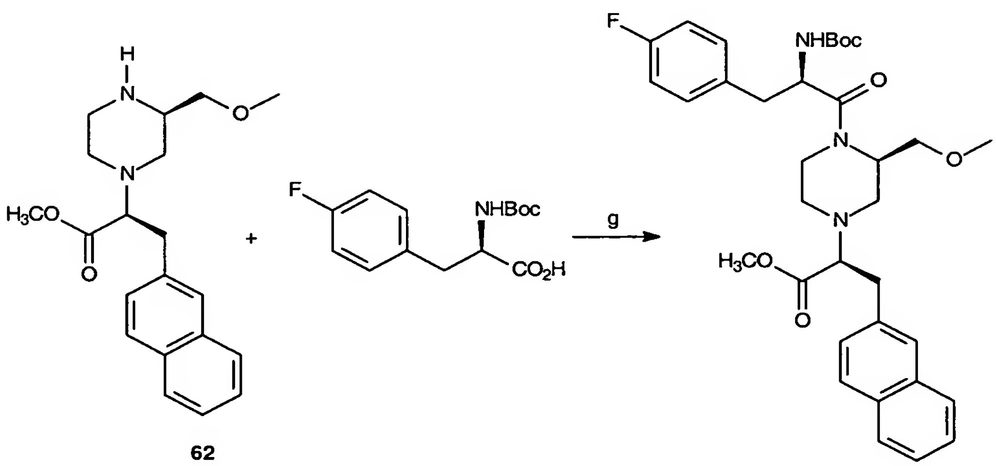
Reagents and conditions: (e) BH_3/THF, THF; 0 °C, 18 hr.



61

62

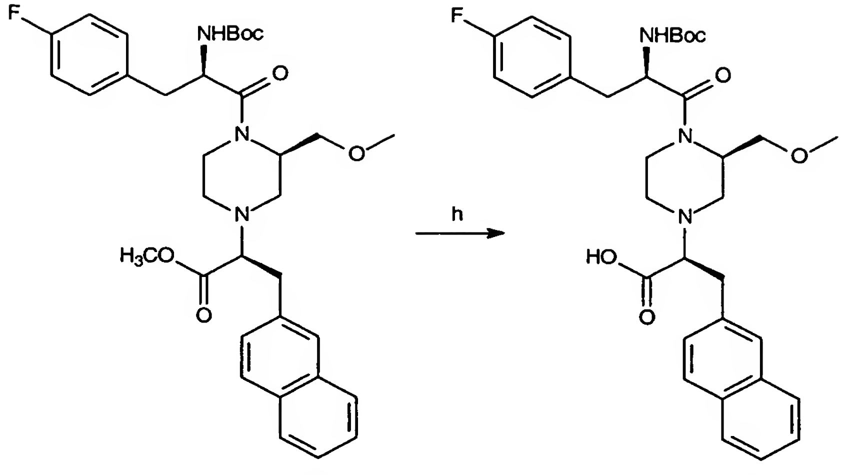
Reagents and conditions: (f) 4-mercaptophenol, K_2CO_3, DMF; rt, 5 hr.



62

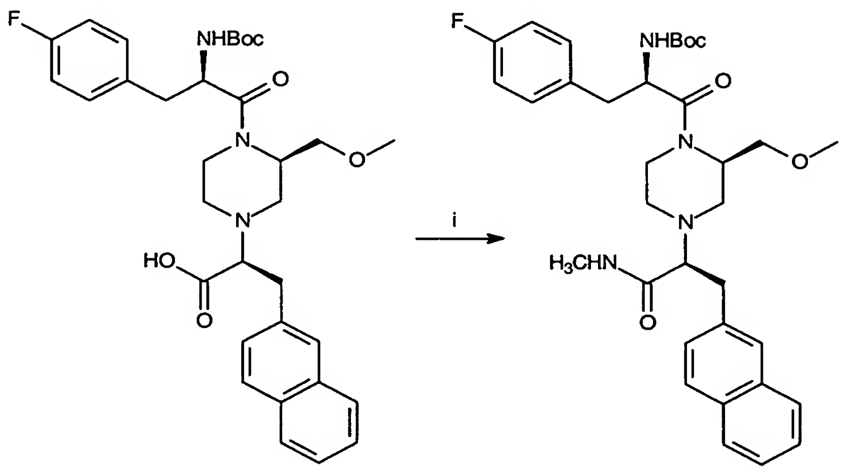
63

Reagents and conditions: (g) HATU, NMM, DMF; rt, 30 hr.



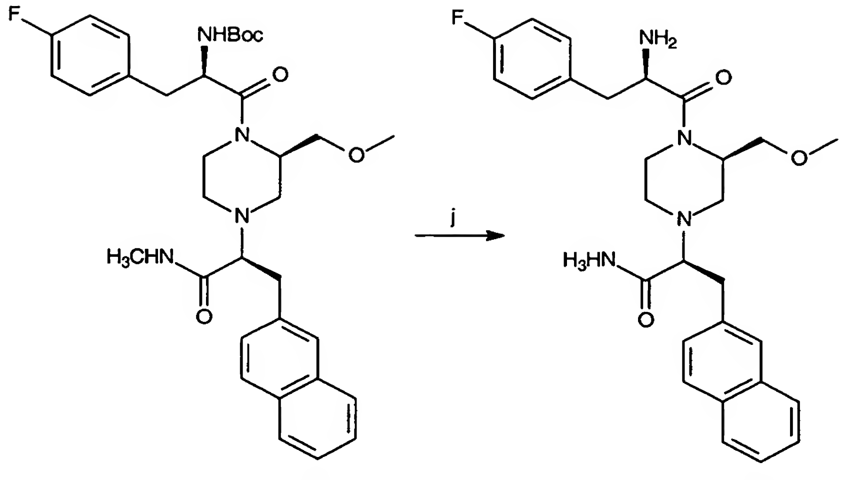
63 64

Reagents and conditions: (h) LiOH THF/H_2O; rt, 18 hr.



64 65

Reagents and conditions: (i) CH_3NH_2, PyBOP, TEA, CH_2Cl_2; 0 °C, 18 hr.



65 **66**

Reagents and conditions: (j) TFA/anisole/CH_2Cl_2; rt, 1 hr.

EXAMPLE 17

2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide (66)

Preparation of 2-(2-*tert*-butoxycarbonylamino-3-methoxy-propionylamino)-3-naphthalen-2-yl-propionic acid methyl ester (57): Naphthylen-2-ylacetic acid methyl ester HCl (3.3g, 12.5 mmol), 3-methoxy-2-*N*-Boc-aminopropionic acid (2.7g, 12.5 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (3.4g, 25.0 mmol) and 1-hydroxybenzotriazole (2.8g, 15.0 mmol) are dissolved in anhydrous DMF (10 mL). This reaction mixture is cooled to 0 °C, then N-methylmorpholine (4.1 mL, 37.5 mmol) is added. This reaction mixture is placed in the refrigerator overnight. EtOAc (75 mL) and water (500 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (2 x 75 mL). The organic layers are combined and washed with water (100 mL), and dried over Na_2SO_4. The solution is concentrated in vacuo to afford 5.2g (97% yield) of the desired product. ^{1}H NMR (3000 MHz, $CDCl_3$, δ): 7.84-7.72 (m, 3H), 7.60 (s,1H), 7.50-7.40 (m, 2H), 7.28-7.20 (m, 1H), 5.40 (br s, 1H), 4.94 (quartet, 9.0 Hz, 1H), 4.24 (br s, 1H), 3.80(m, 1H), 3.72 (s, 3H), 3.42 (m, 1H), 3.30 (m, 1H), 3.24 (s, 3H), 1.41 (s, 9H); ^{13}C NMR, δ 171.8, 170.4, 155.3, 133.7, 133.6, 132.7, 128.4, 127.9, 127.7, 126.4, 126.0, 80.3, 72.2, 59.1, 54.0, 53.6, 52.6, 38.1, 28.5.

Preparation of 2-(2-amino-3-methoxy-propionylamino)-3-naphthalen-2-yl-propionic acid methyl ester HCl (58): 2-(2-*tert*-butoxycarbonylamino-3-methoxy-propionylamino)-3-naphthalen-2-yl-propionic acid methyl ester, **57**, (5.2g, 12.1 mmol) is dissolved in 4M hydrogen

chloride in dioxane (40mL) and stirred at room temperature for 1 hour. 1,2- Dichloroethane (40 mL) is added. The solution is concentrated *in vacuo* to afford 4.43 g (quantitative yield) of the desired product.

Preparation of 2-[3-methoxy-2-(2-nitro-benzenesulfonylamino)-propionylamino]-3-naphthalen-2-yl-propionic acid methyl ester (59): 2-(2-Amino-3-methoxy-propionylamino)-3-naphthalen-2-yl-propionic acid methyl ester, **58**, (4.43g, 12.1 mmol) and 2-nitrobenzene sulfonyl chloride (2.8g, 12.7 mmol) are dissolved in any THF (20 mL). The mixture is cooled to 0 °C and triethyl amine (5 mL) is added to the reaction mixture which is then allowed to stir overnight at room temperature. Water (100 mL) is added and the reaction mixture pH adjusted to 3 with 1M $KHSO_4$. The solution is extracted with EtOAc (3 x 100 mL) and the organic layers are combined and dried over Na_2SO_4. The solvent is removed in vacuo to afford 6.4 g (quantitative yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.02 (m, 1H), 7.8 (m, 4H), 7.60 (m, 3H), 7.48 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 6.25 Hz, 1H), 4.57 (quartet, J = 6.25 Hz, 1H), 4.02 (quartet, J = 6.25 Hz, 1H), 3.70 (s, 3H), 3.47 (m, 2H), 3.44 (m, 2H), 3.49 (s, 3H); ^{13}C NMR, δ 171.5, 168.7, 147.9, 134.2, 133.6, 133.5, 133.2, 132.7, 131.0, 128.4, 128.3, 127.9, 127.5, 126.5, 126.1, 125.9, 72.3, 59.1, 56.6, 53.8, 52.7, 38.0.

Preparation of 2-[3-methoxymethyl-4(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester (60): 1,2-Dibromoethane (11 mL, 125 mmol) and K_2CO_3 (15.5g, 112.3 mmol) are added to a 2-[3-methoxy-2-(2-nitro-benzenesulfonylamino)-propionylamino]-3-naphthalen-2-yl-propionic acid methyl ester, **59**, (6.4g, 12.4 mmol) solution in anhydrous DMF (30 mL). The reaction mixture is stirred at 60 °C overnight. The reaction mixture is cooled to room temperature and the pH is adjusted to 3 with 1M $KHSO_4$. The solution is extracted with EtOAc (3 x 100 mL) and the organic layers are combined and dried over Na_2SO_4. The solvent is removed in vacuo to afford 5.6g (85% yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.89 (m, 1H), 7.70 (m, 3H), 7.57 (m, 3H), 7.47 (m, 1H), 7.41 (m, 2H), 7.30 (d, J = 8.6 Hz, 1H), 5.39 (m, 1H), 4.37 (s, 3H), 3.62 (m, 4H), 3.46 (m, 2H), 3.35 (m, 1H), 3.20 (m, 2H), 3.13 (s, 3H); ^{13}C NMR, δ 170.4, 165.7, 156.5, 147.9, 134.2, 134.1, 133.6, 133.4, 132.6, 132.4, 130.8, 128.4, 127.8, 127.7, 127.2, 126.4, 126.0, 124.6, 74.1, 65.0, 58.9, 58.1, 52.7, 44.3, 41.8, 34.3.

Preparation of 2-[3-methoxymethyl-4-(2-nitro-benzenesulfonyl)-piperazine-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester (61): To a solution of 2-[3-methoxymethyl-4(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester, **60**, (5.6g, 10.4 mmol) in anhydrous THF (10 mL) is added 1.0M borane-tetrahydrofuran complex (31.2 mL) at –20 °C. The reaction mixture is stirred at this temperature overnight. Methanol (3 mL)

is added to the reaction mixture at –20 °C and allowed to stir for twenty minutes. Additional methanol (6 mL) is and the reaction mixture is allowed to warm to the room temperature. The solvent is removed *in vacuo* and the product purified over silica (EtOAc/Hexane , 1:1) to afford 3.5 g (64% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 8.05 (m, 1H), 7.75 (m,3H), 7.62 (m, 4H), 7.50 (m, 2H), 7.30 (dd, J = 8.4, 2.1 Hz, 1H), 3.94 (t, J = 6.3 Hz, 1H), 3.66 (s, 3H), 3.58 (t, J = 6.8 Hz, 1H), 3.30-2.95 (m, 7H), 2.82 (s, 3H), 2.79 (m, 2H), 2.40 (dt, J = 12.7, 4.3 Hz, 1H); ^{13}C NMR, δ 171.8, 148.0, 136.0, 134.1, 133.7, 132.4, 132.0, 131.5, 128.1, 127.9, 127.7, 126.3, 125.8, 124.5, 69.5, 68.7, 58.7, 53.8, 52.8, 51.6, 46.6, 42.8, 35.4.

Preparation of 2-(3-methoxymethyl-piperazine-1yl)-3-naphthalen2-yl-propionic acid methyl ester (62): To a solution of 2-[3-methoxymethyl-4-(2-nitro-benzenesulfonyl)-piperazine-1-yl]-3-naphthalen-2-yl-propionic acid methyl ester, **61**, (3.5g, 6.67 mmol) in anhydrous DMF (40 mL) is added potassium carbonate (5.5g, 40.0 mmol) and 4-mercaptophenol (2.5g, 20.0 mmol). The reaction mixture is stirred for six hours at room temperature, then cooled in a ice bath and pH is adjusted to 3 with 1M HCl. The reaction mixture is extracted with Et_2O (4x100 mL). All organic layers are combined and extracted with 1M HCl (100 mL). All aqueous layers are combined and cooled in a ice bath and the pH is adjusted to 10 with K_2CO_3. The aqueous layer is extracted with EtOAc (4 x 125 mL) and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford2.2 g (97% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.85 - 7.78 (m, 3H), 7.65 (s, 1H), 7.54 – 7.40 (m, 2H), 7.35 (dd, J = 7.2, 2.4Hz, 1H), 3.59 (s, 3H), 3.56 (dd, J = 6.0, 2.5 Hz, 1H), 3.40 – 3.10 (m, 5H), 3.38 (s, 3H), 3.05 – 2.78 (m, 5H), 2.59 (dt, J = 7.2, 2.5 Hz, 1H), 2.20 (t, J = 10.8 Hz, 1H); ^{13}C NMR, δ 171.8, 135.9, 133.7, 132.5, 128.2, 127.9, 127.8, 126.2, 125.7, 74.8, 69.9, 59.4, 55.2, 52.3, 51.4, 50.8, 45.6, 35.8.

Preparation of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazine-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester (63): 2-(3-Methoxymethyl-piperazine-1yl)-3-naphthalen2-yl-propionic acid methyl ester, **62**, (2.2g, 6.4 mmol) and N-Boc-(4-flouro)phenylalanine (1.9g, 6.8 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (4.9g, 12.9 mmol) are dissolved in anhydrous DMF (20 mL). This reaction mixture is cooled to 0 °C then N-methylmorpholine (0.75 mL, 6.8 mmol) is added. This reaction mixture is placed in a refrigerator overnight. EtOAc (75 mL) and water (300 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 150 mL). All organic layers are combined and washed with water (100 mL), and dried over Na_2SO_4. The solution is concentrated *in vacuo* and the residue purified over silica (EtOAc/Hexane, 1:1) to afford 3.6 g (92% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.72 – 7.58 (m, 3H), 7.44 (s, 1H), 7.40 – 7.22 (m, 2H), 7.15 (d, J = 8.2 Hz, 1H), 7.10 – 6.98 (m, 2H), 6.82 (t, J = 8.2 Hz, 2H), 5.88 – 5.64 (m, 1H), 4.82 – 4.50 (m, 1.5H), 4.18 (d, J = 12.3 Hz, 0.5H),

3.58 – 3.44 (m, 3H), 3.42 – 3.30 (m, 1.5H), 3.08 – 3.72 (m,10H), 2.68 - 2.45 (m, 2H), 2.40 – 2.18 (m, 1H), 1.70 (d, J = 12.3 Hz, 0.5H), 1.35 – 1.25 (m, 1H), 1.30 (s, 9H); ^{13}C NMR, δ 171.8, 171.4, 170.4, 163.9, 160.2, 153.0,152.8, 136.0, 133.6, 132.6, 132.3, 131.4, 127.9, 127.7, 127.5, 126.2, 125.6, 115.5, 115.2, 115.1, 115.0, 79.5, 79.2, 69.6, 68.9, 68.3, 68.1, 60.3, 58.6, 58.3, 53.7, 52.0, 51.2, 48.8, 46.5, 45.6, 42.3, 40.0, 38.7, 35.3, 28.4.

Preparation of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazine-1-yl}-3-naphthalen-2-yl-propionic acid (64): LiOH (0.71g, 29.7 mmol) is added to the cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazine-1-yl}-3-naphthalen-2-yl-propionic acid methyl ester, **63**, (3.6g, 5.9 mmol) in THF/H_2O (2/1, 60mL). The reaction mixture is stirred for overnight. The reaction mixture is cooled in ice bath and pH is adjusted to 3 with 1M HCl. The aqueous layer is extracted with EtOAc (3 x 100 mL) and dried over Na_2SO_4. The solution is concentrated *in vacuo* to afford 3.7 g 100% yield) of the desired product.

Preparation of {1-(4-fluorobenzyl)-2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2oxo-ethyl}-carbamic acid *tert*-butyl ester (65): To a cold solution of 2-{4-[2-*tert*-butoxycarbonylamino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazine-1-yl}-3-naphthalen-2-yl-propionic acid, **64**, (2.7g, 4.3 mmol) and PyBOP (2.9g, 5.6 mmol) in anhydrous dichloromethane (15 mL) is added 2M methyl amine solution in THF (4.4mL, 8.8 mmol) and triethyl amine (1.5 mL, 10.7 mmol). The reaction mixture is placed in a refrigerator overnight. EtOAc (50 mL) and water (200 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3x100 mL). All organic layers are combined and washed with brine (100 mL), and dried over Na_2SO_4. The solution is concentrated *in vacuo* to afford 2.6 g (100% yield) of the desired product. ^{1}H NMR ($CDCl_3$, δ): 7.62 – 7.50 (m, 3H), 7.45 (s, 1H), 7.35 – 7.12 (m, 3H), 7.05 – 6.92 (m, 2H), 6.82 – 6.70 (m, 2H), 5.45 (dd, J = 20.5, 8.2 Hz, 0.5H), 4.75 – 4.45 (m, 1H), 4.05 (d, J = 12.3 Hz, 0.5H), 3.5 – 3.20 (m, 1H), 3.20 – 3.08 (m, 1H), 3.08 – 2.98 (m, 1H), 2.92 (s, 8H), 2.84 - 2.64 (m, 2H), 2.55 (br s, 2H), 2.40 – 1.85 (m, 1H), 1.6 (s, 7H), 1.22 (d, J = 6.6 Hz, 7H); ^{13}C NMR, δ 171.6, 171.4, 171.2, 170.2, 163.5, 160.3, 154.9, 137.3, 137.2, 132.6, 132.3, 132.1, 131.2, 127.6, 127.5, 126.0, 125.4, 115.4, 115.1, 114.9, 79.5, 79.3, 70.2, 69.6, 69.3, 58.9, 58.8, 53.3, 51.2, 49.8, 49.6, 48.7, 48.3, 46.3, 42.9, 39.8, 38.9, 38.6, 33.6, 28.3, 26.5, 26.4, 25.8, 25.7.

Preparation of 2-{4-[2-amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide HCl (66): {1-(4-Fluoro-benzyl)2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2oxo-ethyl}-carbamic acid *tert*-butyl ester, **65**, is dissolved in 4M HCl in dioxane (60 mL). The reaction

mixture is stirred for 90 minutes then 1,2-dichloroethane (60 mL) is added. The solution is concentrated *in vacuo* to afford 3.6 g (98% yield) of the desired product.

The following are non-limiting examples of analogs which comprise the first aspect of Category V of the present invention.

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.33-7.09 (m, 8H), 4.77-4.20 (m, 2H), 3.58-3.38 (m, 3H), 3.30 (s, 3H), 3.25-2.70 (m, 9H), 2.67, 2.64 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.20-1.65 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.0, 172.5, 170.3, 169.0, 165.9, 162.6, 162.2, 161.7, 138.8, 138.0, 134.0, 133.7, 133.3, 133.2, 132.3, 131.8, 131.5, 129.9, 129.8, 117.5, 117.3, 117.2, 117.1, 71.9, 71.0, 59.9, 59.7, 55.3, 52.6, 52.4, 43.6, 40.1, 38.6, 37.9, 35.3, 26.3; MS *m/z* (ESI): 491 (M + H, 100), 493 (M + 2 + H, 37).

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2-chlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(3-chlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2,4-dichlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-N-methyl-3-naphthalen-2-yl-propionamide;

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2-chlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(3-chlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2,4-dichlorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-chlorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-N-methyl-3-naphthalen-2-yl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2-fluorophenyl)-N-methyl-propionamide;

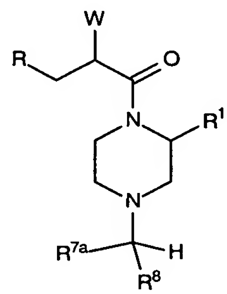
2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(3-fluorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2-fluorophenyl)-N-methyl-propionamide;

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(2,4-difluorophenyl)-N-methyl-propionamide; and

2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-N-methyl-3-naphthalen-2-yl-propionamide.

The second aspect of Category V relates to compounds having the formula:



the first iteration of which relates to W units having the formula –NHC(O)Q wherein R is a substituted or unsubstituted aryl unit as described herein above and non-limiting examples of R^1, R^{7a}, R^8 and Q are provided herein below in Table XVI.

TABLE XVI

No.	R^1	Q	R^{7a}	R^8
300	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
301	ethoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
302	propoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
303	methoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
1337	ethoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
1338	methoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
1339	ethoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	naphthylen-2-ylmethyl
1340	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1341	ethoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1342	propoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1343	methoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1344	ethoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1345	methoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1346	ethoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1347	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl

1348	ethoxymethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1349	propoxymethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1350	methoxyethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1351	ethoxyethyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1352	methoxypropyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1353	ethoxypropyl	2-aminopyrrolidin-5-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1354	methoxymethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1555	ethoxymethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1356	propoxymethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1357	methoxyethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1358	ethoxyethyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1359	methoxypropyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1360	ethoxypropyl	THQ-3-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1361	methoxymethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1362	ethoxymethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1363	propoxymethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1364	methoxyethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1365	ethoxyethyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1366	methoxypropyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1367	ethoxypropyl	THQ-3-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1368	methoxymethyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1369	ethoxymethyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1370	propoxymethyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1371	methoxyethyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1372	ethoxyethyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1373	methoxypropyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1374	ethoxypropyl	THQ-3-yl	-C(O)NH_2	(4-chlorophenyl)methyl
1375	methoxymethyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1376	ethoxymethyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1377	propoxymethyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1378	methoxyethyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1379	ethoxyethyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1380	methoxypropyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1381	ethoxypropyl	pyrrolidin-2-yl	-C(O)NH_2	naphthylen-2-ylmethyl
1382	methoxymethyl	pyrrolidin-2-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl
1383	ethoxymethyl	pyrrolidin-2-yl	-C(O)NH_2	(3,4-dichlorophenyl)methyl

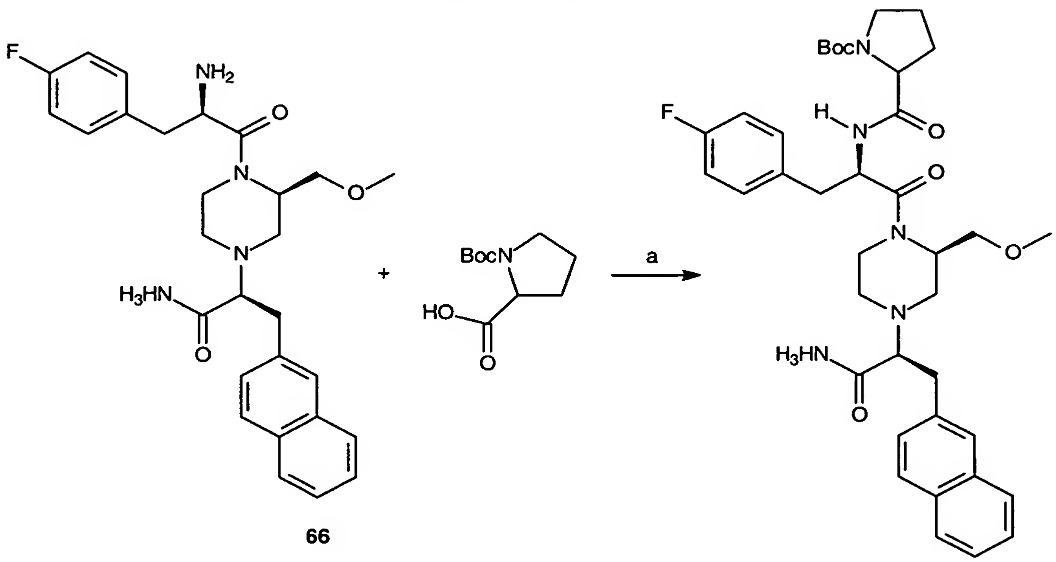
1384	propoxymethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1385	methoxyethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1386	ethoxyethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1387	methoxypropyl	pyrrolidin-2-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1388	ethoxypropyl	pyrrolidin-2-yl	$-C(O)NH_2$	(3,4-dichlorophenyl)methyl
1389	methoxymethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1390	ethoxymethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1391	propoxymethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1392	methoxyethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1393	ethoxyethyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1394	methoxypropyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1395	ethoxypropyl	pyrrolidin-2-yl	$-C(O)NH_2$	(4-chlorophenyl)methyl
1396	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1397	ethoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1398	propoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1399	methoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1400	ethoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1401	methoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1402	ethoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1403	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1404	ethoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1405	propoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1406	methoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1407	ethoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1408	methoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1409	ethoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(3,4-dichlorophenyl)methyl
1410	methoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1411	ethoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1412	propoxymethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1413	methoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1414	ethoxyethyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1415	methoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1416	ethoxypropyl	2-aminopyrrolidin-5-yl	$-C(O)NHCH_3$	(4-chlorophenyl)methyl
1417	methoxymethyl	THQ-3-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1418	ethoxymethyl	THQ-3-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl
1419	propoxymethyl	THQ-3-yl	$-C(O)NHCH_3$	naphthylen-2-ylmethyl

1420	methoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1421	ethoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1422	methoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1423	ethoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1424	methoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1425	ethoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1426	propoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1427	methoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1428	ethoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1429	methoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1430	ethoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1431	methoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1432	ethoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1433	propoxymethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1434	methoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1435	ethoxyethyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1436	methoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1437	ethoxypropyl	THQ-3-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1438	methoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1439	ethoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1440	propoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1441	methoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1442	ethoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1443	methoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1444	ethoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	naphthylen-2-ylmethyl
1445	methoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1446	ethoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1447	propoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1448	methoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1449	ethoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1450	methoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1451	ethoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(3,4-dichlorophenyl)methyl
1452	methoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1453	ethoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1454	propoxymethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1455	methoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl

1456	ethoxyethyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1457	methoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl
1458	ethoxypropyl	pyrrolidin-2-yl	-C(O)NHCH$_3$	(4-chlorophenyl)methyl

The compounds of the second aspect of Category V can be suitably prepared by the procedure outlined herein below in Scheme XVIII beginning with compounds which comprises the first aspect of this Category, for example, compound **66**.

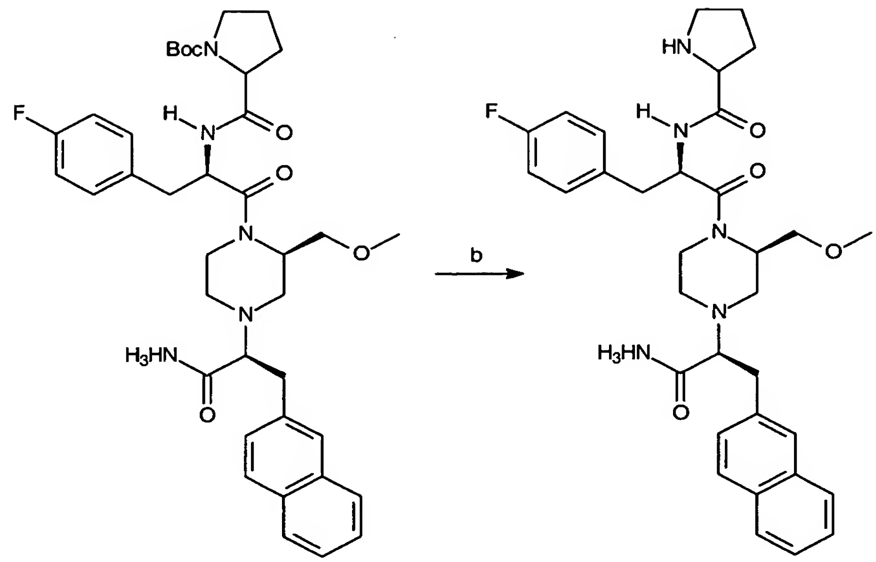
Scheme XVIII



66

67

Reagents and conditions: (a) WDCI, HOBt, NMM, DMF; 0 °C, 18 hr.



67 68

Reagents and conditions: (b) 4 N HCl, dioxane; rt, 1 hr.

EXAMPLE 18

Pyrrolidine-2-carboxylic acid {1-(4-fluoro-benzyl)-2-[2-methoxymethyl-4-(1-methyl carbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide (68)

Preparation of 2-{1-(4-fluorobenzyl)-2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (67): 2-{4-[2-Amino-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide HCl, **66**, (0.36g, 0.55 mmol) and BOC-L-Proline (0.13g, 0.6 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.2g, 1.1 mmol) and 1-hydroxybenzotriazole (0.1 g, 0.7 mmol) are dissolved in anhydrous DMF (1.5 mL). The reaction mixture is cooled to 0 °C, then N-methylmorpholine (0.5 mL, 4.1 mmol) is added. The reaction mixture is placed in a refrigerator overnight. EtOAc (25 mL) and water (75 mL) are added, and the organic layer is separated. The aqueous layer is extracted with EtOAc (3 x 30 mL). All organic layers are combined and washed with water (2 x 50 mL), and dried over Na_2SO_4. The solvent is removed *in vacuo* to afford 0.39 g of the desired product.

Preparation of pyrrolidine-2-carboxylic acid {1-(4-fluorobenzyl)-2-[2-methoxy-methyl-4-(1-methyl carbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide (68): Crude 2-{1-(4-fluorobenzyl)-2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester, **67**, is dissolved in 4M hydrogen chloride in dioxane (10 mL) and stirred at room temperature for 1 hour. 1,2- dichloroethane (10 mL) is added. Removal of solvents in vacuo gives the crude hydrogen

chloride salt of product which is then purified by preparative HPLC to afford 0.22 g (54% yield) of the desired product as the trifluoroacetate salt. A small amount of product is converted into free base by treating with $NaHCO_3$ to obtain NMR spectra. ^1H NMR ($CDCl_3$, δ): 7.80 – 7.60 (m, 4H), 7.45 – 7.25 (m, 3H), 7.18 – 7.00 (m, 2H), 7.00 – 6.85 (m, 2H), 6.32 – 6.28 (m, 0.5H), 5.08 – 4.92 (m, 1H), 4.78 – 4.69 (,0.5H), 4.10 (d, J = 13.0Hz, 0.5H), 3.70 – 3.58 (m, 1H), 3.58 – 3.15 (m, 8H), 2.98 – 2.46 (m, 11H), 2.28 – 2.15 (m, 0.5H), 2.15 – 1.50 (m, 8H). HRFAB(positive) m/e 604.3299 calculated for $C_{34}H_{42}FN_5O_4$ $(M+H)^+$, Found 604.3292.

The following are non-limiting examples of other compounds according to the various aspects of Category V.

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-methoxymethyl-piperazine-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]-amide: ^1H NMR (CD_3OD, δ): 7.47 – 7.41 (m, 2H), 7.28 – 7.25 (m, 2H), 7.16 – 7.12 (m, 1H), 7.08 – 7.02 (m, 2H), 5.11 (t, J = 15.0 Hz, 1H), 4.63 (br s, 0.5H), 4.25 (d, J = 13.5 Hz, 0.5H), 3.95 (d, J = 12.9 Hz, 0.5H0, 3.74 – 3.66 (m, 0.5H), 3.58 (t, J = 6.3 Hz, 0.5H), 3.47 – 3.40 (m, 0.5H), 3.38 – 3.30 (m, 1H), 3.32 (s, 3H), 3.26 – 3.17 (m, 4H), 3.02 – 2.89 (m, 6.5H), 2.80 – 2.68 (m, 4H), 2.53 – 2.46 (m, 1H), 2.12 (t, J = 11.1 Hz, 0.5H), 1.70 – 1.51 (m, 2H), 1.46 – 1.31 (m, 3H). HRFAB(positive) m/e 608.220664 calculated for $C_{29}H_{36}Cl_2FN_5O_4$ $(M+H)^+$, Found 608.218817.

Pyrrolidine-2-carboxylic acid[2-{4-[2-(3,4-dichlorophenyl)-1-methylcarbamoyl-ethyl]-2-methoxymethyl-piperazin-1-yl}-1-(4-fluorobenzyl)-2-oxo-ethyl]amide: ^1H NMR (CD_3OD, δ): 7.46 – 7.42 (m,2H), 7.32 – 7.26 (m, 2H), 7.17 – 7.14 (m, 1H), 7.09 – 7.04 (m, 2H), 5.17 (t, J = 8.1 Hz, 1H), 4.65 (br s, 0.5H), 4.27 – 4.23 (m, 2H), 4.0 (m, 0.5H), 3.80 (bs, 0.5H), 3.57 (t, J = 9.3 Hz, 0.5H), 3.45 – 3.20 (m, 10H), 3.09 – 2.89 (m, 6H), 2.78 – 2.68 (m, 3H), 2.52 – 2.28 (m, 2H), 2.20 – 1.72 (m, 4H); HRFAB(positive) m/e 622.236314 calculated for $C_{30}H_{38}Cl_2FN_5O_4$ $(M+H)^+$, Found 622.234445

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-methoxy- methylpiperazin-1-yl}-N-methyl-3-naphthalen-2yl-propionamide: ^1H NMR ($CDCl_3$, δ): 8.08 (t, J = 6.7 Hz, 1H), 7.74 – 7.64 (m, 3H), 7.40 – 7.25 (m, 3H), 7.10 – 7.04 (m, 2H), 6.95 – 6.88 (m, 2H), 4.98 (quartet, J = 6.7 Hz, 1H), 4.84 (quartet, J = 6.7 Hz, 1H), 4.68 – 4.58 (m, 1H), 4.18 – 4.12 (m, 1H), 3.65 – 3.55 (m, 1H), 3.46 – 3.30 (m, 4H), 3.28 – 3.20 (m, 3H), 2.95 – 2.70 (m, 5H), 2.78 – 2.60 (m, 5H), 2.58 – 2.45 (m, 2H), 2.20 – 2.02 (m, 2H), 1.65 (dd, J = 10.6, 3.99 Hz, 1H), 1.25 – 1.22 (m, 4H);HRFAB(positive) m/e 592.3299 calculated for $C_{33}H_{42}FN_5O_4$ $(M+H)^+$, Found 592.3354.

{1-(4-Fluorobenzyl)-2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid methyl ester: ^{1}H NMR ($CDCl_3$, δ): 7.75- - 7.6 (m, 3H), 7.58 (s, 1H), 7.50 – 7.42 (m, 2H), 7.42 – 7.38 (m, 1H), 7.08 – 7.00 (m, 2H), 6.90 – 6.82 (m, 2H), 5.55 (t, J = 8.2 Hz, 0.5H), 4.82 – 4.68 (m, 1H), 4.62 – 4.55 (m, 0.5H), 4.15 (d, J = 13.0 Hz, 0.5H), 3.58 (s, 2H), 3.52 (m, 2H), 3.43 – 3.28 (m, 3H), 3.28 – 3.20 (m, 3H), 3.15 (2H), 2.98 – 2.72 (m, 4H), 2.72 – 2.58 (m, 4H), 2.58 – 2.42 (m, 1H), 2.32 – 2.20 (m, 0.5H), 2.12 – 2.00 (m, 0.5H), 1.60 (dd, J = 13.0, 2.6 Hz, 0.5H); HRFAB(positive) m/e 565.2826 calculated for $C_{31}H_{37}FN_4O_5$ $(M+H)^+$, Found 565.2806; Elemental Analysis: calculated for $C_{31}H_{37}FN_4O_5$. (1.23 TFA) (MW. 704.57): C 57.01%, H 5.47%, N 7.95%, Found: C 57.03%, H 5.33%, N 7.97%.

2-{4-[3-(4-Fluorophenyl)-2-(2-hydroxy-2-methyl-propionylamino)-propionyl]-3-methoxy methyl-piperazin-1-yl}-N-methyl-3-naphthalen-2-yl-propionamide. ^{1}H NMR ($CDCl_3$, δ): 8.08 – 7.95 (m, 3H), 7.88 (d, J = 9.4 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.52 (d, J = 9.4 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.21 (t, J = 4.7 Hz, 2H_), 5.28 – 5.18 (m, 1H), 5.15 – 4.98 (m, 2H), 5.02 (s, 3H), 4.55 (d, J = 9.4 Hz, 0.5H), 4.28 (d, J = 9.4 Hz, 0.5H), 4.15 – 4.05 (m, 1H), 3.92 – 3.05 (m, 12.5H), 2.85 – 2.62 (m, 3H), 2.20 (d, J = 7.0 Hz, 0.5H), 2.02 – 1.95 (m, 1H), 1.52 – 1.40 (m, 5H); HRFAB(positive) m/e 593.3139 calculated for $C_{33}H_{41}FN_4O_5$ $(M+H)^+$, Found 593.3157; Elemental Analysis: calculated for $C_{33}H_{41}FN_4O_5$. (1.28 TFA) (MW. 738.51): C 57.83%, H 5.77%, N 7.59%, Found: C 57.83%, H 5.70%, N 7.77%.

{1-(4-Fluoro-benzyl)-2-[2-methoxymethyl-4-(1-methylcarbamoyl-2-maphthalen-2-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid ethyl ester. ^{1}H NMR ($CDCl_3$, δ): 7.72 – 7.64 (m, 3H), 7.5 (s, 1H), 7.36 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.06 – 7.02 (m, 2H), 6.90 – 6.72 (dt, J = 9.8, 2.6 Hz, 2H), 6.33(s, 0.5H), 5.50 – 5.45 (m, 1H), 5.25 (s, 3H), 4.82 – 4.60 (m, 1.5H), 4.20 – 3.98 (m, 2H), 3.58 – 3.49 (m, 1H), 3.48 – 3.35 (m, 6H), 3.30 – 3.18 (m, 4H), 2.96 – 2.84 (m, 3H), 2.75 – 2.62 (m, 3.5H), 2.58 – 2.44 (m, 1H), 2.28 – 2.20 (m, 0.5H), 2.12 – 1.98 (m, 0.5H), 1.59 (d, J = 9.8Hz, 0.5H); HRFAB(positive) m/e 579.2982 calculated for $C_{32}H_{39}FN_4O_5$ $(M+H)^+$, Found 579.2980; Elemental Analysis: calculated for $C_{32}H_{39}FN_4O_5$. (0.95 TFA) (MW. 686.61): C. 59.29%, H 5.86%, N 8.16%, Found: C 59.29%, H 5.98%, N 8.14%.

2-{4-[2-(2-Amino-2-methyl-propionylamino)-3-(4-fluorophenyl)-propionyl]-3-methoxymethyl-piperazin-1-yl}-3-(4-chlorophenyl)-N-methyl-propionamide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.55-7.42 (m, 6H), 7.29 (m, 2H), 5.34 (t, 1H, *J* = 7.6 Hz), 5.00-4.60 (m, 1H), 4.35-4.13 (m, 1H), 3.93-3.82 (m, 1H), 3.65 (m, 2H), 3.52, 3.50 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.45-3.05 (m, 8H), 2.89, 2.85 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.68-2.16 (m, 1H), 1.79, 1.74, 1.69 (3 singlets, 6H, $NH_2C(CH_3)_2C(O)$, rotamers); ^{13}C NMR (CD_3OD, with rotamers) δ 173.2, 173.0, 172.5, 171.9, 171.3, 165.5, 162.4, 162.2, 161.9, 137.8, 137.0, 134.3,

134.1, 134.0, 133.0, 132.9, 132.8, 132.4, 130.1, 129.9, 119.9, 117.0, 116.8, 116.5, 72.7, 72.1, 70.0, 59.8, 59.7, 58.5, 54.4, 52.6, 52.4, 52.0, 50.8, 43.4, 39.8, 39.2, 38.0, 35.1, 35.0, 26.4, 24.6, 24.3; MS *m/z* (ESI): 576 (M + H, 100), 578 (M + 2 + H, 37).

Pyrrolidine-2-carboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methylcarbamoyl-ethyl]-2-methoxymethyl-piperazin-1-yl}-1-(4-fluoro-benzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.55-7.43 (m, 6H), 7.29 (m, 2H), 5.39 (t, 1H, J = 7.7 Hz), 5.06-4.58 (m, 1H), 4.48 (t, 1H, J = 7.2 Hz), 4.40-4.22 (m, 1H), 3.94-3.82 (m, 2H), 3.67 (m, 2H), 3.54, 3.51 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.49 (m, 2H), 3.24 (m, 6H), 2.90, 2.86 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.73-2.56 (m, 2H), 2.27-2.01 (m, 4H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.5, 171.8, 171.7, 169.4, 169.1, 164.4, 162.8, 162.0, 137.9, 137.0, 134.0, 133.7, 132.7, 132.6, 132.2, 132.1, 129.8, 129.6, 116.7, 116.5, 116.4, 116.3, 72.3, 71.7, 70.7, 61.1, 59.6, 59.5, 54.4, 52.1, 52.0, 51.9, 51.8, 50.5, 50.0, 47.5, 43.3, 39.6, 39.3, 38.2, 34.8, 31.4, 31.3, 26.2, 26.1 25.1, 25.0; MS *m/z* (ESI): 588 (M + H, 100), 590 (M + 2 + H, 37).

1-Amino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methyl-carbamoyl-ethyl]-2-methoxymethyl-piperazin-1-yl}-1-(4-fluoro-benzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.41-7.26 (m, 6H), 7.17 (m, 2H), 5.18 (t, 1H, J = 7.8 Hz), 4.83-4.38 (m, 1H), 4.18-3.93 (m, 1H), 3.72 (m, 1H), 3.45 (m, 2H), 3.36, 3.35 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.24-2.89 (m, 8H), 2.75, 2.72 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.45-1.95 (m, 1H), 1.74-1.43 (m, 4H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.0, 172.4, 172.2, 171.6, 171.0, 170.5, 165.5, 162.4, 162.2, 138.3, 137.4, 134.2, 132.9, 132.8, 132.7, 132.4, 130.0, 129.9, 117.1, 116.8, 116.5, 72.4, 71.7, 71.0, 59.8, 59.7, 54.7, 52.5, 52.4, 52.0, 50.6, 43.6, 40.1, 39.1, 37.9, 36.7, 35.1, 26.4, 13.9, 13.8; MS *m/z* (ESI): 574 (M + H, 100), 576 (M + 2 + H, 37).

1-Methylamino-cyclopropanecarboxylic acid [2-{4-[2-(4-chlorophenyl)-1-methyl-carbamoyl-ethyl]-2-methoxymethyl-piperazin-1-yl}-1-(4-fluoro-benzyl)-2-oxo-ethyl]-amide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.46-7.31 (m, 6H), 7.19 (dd, 2H, J = 15.6, 7.0 Hz), 5.26 (m, 1H), 4.86-4.42 (m, 1H), 4.18-3.98 (m, 1H), 3.73 (m, 2H), 3.41, 3.40 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.21-3.07 (m, 8H), 2.87 (m, 1H), 2.84, 2.83 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.80, 2.78 (2 singlets, 3H, $CH_3NHC(CH_2\text{-}CH_2)C(O)$, rotamers), 2.43-1.97 (m, 1H), 1.80-1.61 (m, 4H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.9, 172.3, 172.1, 171.4, 169.8, 165.5, 162.2, 138.3, 137.4, 134.2, 133.0, 132.9, 132.7, 132.4, 130.0, 129.9, 117.0, 116.8, 116.5, 113.6, 72.5, 71.8, 71.0, 59.7, 54.7, 52.4, 52.0, 50.7, 44.1, 43.6, 40.1, 39.1, 37.9, 35.1, 33.2, 26.4, 13.7; MS *m/z* (ESI): 588 (M + H, 100), 590 (M + 2 + H, 37).

3-(4-Chlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-methylamino-propionyl]-3-methoxymethyl-piperazin-1-yl}-N-methyl-propionamide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.32-7.08 (m, 8H), 4.65 (m, 1H), 4.27 (m, 1H), 3.57 (m, 2H), 3.26 (s, 3H), 3.25-2.84 (m, 8H), 2.69, 2.68 (2 singlets, 3H, $CH_3NHC(O)$, rotamers), 2.64 (s, 3H), 2.44 (m, 1H), 2.09 (m, 1H), 1.31 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.0, 169.0, 165.9, 162.7, 139.0, 138.1, 133.6, 133.5, 133.4, 132.3, 131.4, 129.9, 129.7, 117.6, 117.3, 117.1, 71.8, 71.6, 70.9, 60.4, 59.6, 59.4, 55.5, 52.4, 50.7, 43.6, 40.0, 38.3, 37.1, 35.3, 33.1, 32.7, 26.3; MS *m/z* (ESI): 505 (M + H, 100), 507 (M + 2 + H, 37.

3-(4-Chlorophenyl)-N-(2-fluoro-ethyl)-2-{4-[3-(4-fluorophenyl)-2-methylamino-propionyl]-3-methoxymethyl-piperazin-1-yl}-propionamide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.40-7.17 (m, 8H), 4.75 (m, 1H), 4.56-4.29 (m, 2H), 3.70-3.26 (m, 8H), 3.38, 3.35 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.07-2.92 (m, 4H), 2.77, 2.72 (2 singlets, 3H, $\underline{CH_3}NHC(4\text{-}F\text{-}Bn)C(O)$, rotamers), 2.57 (m, 1H), 2.22 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 172.8, 168.8, 139.0, 133.6, 133.4, 133.3, 132.3, 131.3, 129.8117.6, 117.3, 84.6, 82.4, 71.7, 70.9, 60.5, 59.4, 55.5, 51.8, 43.7, 41.2, 41.0, 40.1, 38.2, 34.7, 33.1; MS *m/z* (ESI): 537 (M + H, 100), 539 (M + 2 + H, 37).

3-(4-Chlorophenyl)-2-{4-[3-(4-fluorophenyl)-2-methylamino-propionyl]-3-methoxy-methyl-piperazin-1-yl}-N-(2,2,2-trifluoroethyl)-propionamide: ^{1}H NMR (CD_3OD, with rotamers) δ 7.42-7.03 (m, 8H), 4.75 (m, 1H), 4.19 (m, 1H), 4.83 (m, 2H), 3.54 (m, 2H), 3.35-3.16 (m, 2H), 3.22, 3.21 (2 singlets, 3H, CH_3OCH_2, rotamers), 3.10 (m, 1H), 3.93-2.76 (m, 5H), 2.61, 2.58 (2 singlets, 3H, $CH_3NHC(4\text{-}F\text{-}Bn)C(O)$, rotamers), 2.38 (m, 1H), 2.11 (m, 1H), 1.30 (m, 1H); ^{13}C NMR (CD_3OD, with rotamers) δ 173.5, 168.8, 165.9, 162.7, 138.9, 138.7, 133.6, 133.5, 133.4, 132.3, 131.4, 129.8, 128.0, 124.3, 117.6, 117.3, 117.0, 113.3, 71.6, 71.0, 70.8, 60.4, 59.5, 59.4, 55.4, 52.6, 51.4, 51.2, 43.9, 41.5, 41.0, 40.1, 38.2, 35.1, 34.1, 33.1; MS *m/z* (ESI): 573 (M + H, 100), 575 (M + 2 + H, 37).

FORMULATIONS

The present invention also relates to compositions or formulations which comprise the melanocortin receptor ligands according to the present invention. In general, the compositions of the present invention comprise:

a) an effective amount of one or more melanocortin receptor ligands according to the present invention; and

b) one or more pharmaceutically acceptable excipients.

The compositions of this invention are typically provided in unit dosage form. For the purposes of the present invention the term "unit dosage form" is defined herein as

comprising an effective amount of one or more melanocortin receptor ligands. The compositions of the present invention contain in one embodiment from about 1 mg to about 750 mg of one or more melanocortin receptor ligands, while in other embodiments the compositions comprise from about 3 mg to about 500 mg, or from about 5 mg to about 300 mg respectively.

For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

Non-limiting examples of substances which can serve as pharmaceutically-acceptable excipients or components thereof are sugars, *inter alia*, lactose, glucose and sucrose, sorbitol, mannitol; starches, *inter alia*, corn starch and potato starch; cellulose and its derivatives, *inter alia*, sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; vegetable oils, propylene glycol, glycerin, and polyethylene glycol; agar; alginic acid; wetting agents and lubricants, *inter alia*, sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and buffers.

Standard pharmaceutical formulation techniques are disclosed in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., latest edition and *Peptide and Protein Drug Delivery*, Marcel Dekker, NY, 1991. Dosage forms useful for making the compositions of the present invention or which are compatible with the methods of use as described herein below are described in the following references, all incorporated by reference herein: *Modern Pharmaceutics*, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms* 2d Edition (1976); *Standard-Release Injectable Products*, ed. J. Senior and M. Radomsk, Interpharm Press; Denver, Co. (2000)

The present invention further relates to forms of the present compounds, which under normal human or higher mammalian physiological conditions, release the compounds described herein. One iteration of this aspect includes the pharmaceutically acceptable salts of the analogs described herein. The formulator, for the purposes of compatibility with delivery mode, excipients,

and the like, can select one salt form of the present analogs over another since the compounds themselves are the active species which mitigate the disease processes described herein.

Related to this aspect are the various precursor or "pro-drug" forms of the analogs of the present invention. It may be desirable to formulate the compounds of the present invention as a chemical species which itself is not a melanocortin receptor ligand as described herein, but instead are forms of the present analogs which when delivered to the body of a human or higher mammal will undergo a chemical reaction catalyzed by the normal function of the body, *inter alia*, enzymes present in the stomach, blood serum, said chemical reaction releasing the parent analog. Or alternatively, said "pro-drug" form may cross the blood/brain barrier before undergoing a change which releases the melanocortin receptor ligand in its active form. The term "pro-drug" relates to these species which are converted *in vivo* to the active pharmaceutical.

METHOD OF USE

The present invention also relates to a method for controlling one or more melanocortin receptor, MC-3 or MC-4, mediated or melanocortin receptor modulated mammalian diseases or conditions, said method comprising the step of administering to a human or higher mammal an effective amount of a composition comprising one or more of the melanocortin receptor ligands according to the present invention.

Because the melanocortin receptor ligands of the present invention can be delivered in a manner wherein more than one site of control can be achieved, more than one disease state can be modulated at the same time. Non-limiting examples of diseases which are affected by an antagonist or agonist which stimulates the MC-3 or MC-4 receptor, obesity and other body weight disorders, *inter alia*, anorexia and cachexia. Utilizing the melanocortin receptor ligands of the present invention will therefore affect a variety of diseases, disease states, conditions, or syndromes resulting from body weight disorders, *inter alia*, insulin resistance, glucose intolerance, Type-2 diabetes mellitus, coronary artery disease, elevated blood pressure, hypertension, dyslipidaemia, cancer (e.g., endometrial, cervical, ovarian, breast, prostate, gallbladder, colon), menstrual irregularities, hirsutism, infertility, gallbladder disease, restrictive lung disease, sleep apnea, gout, osteoarthritis, and thromboembolic disease.

MC-3 and MC-4 receptor ligands are also effective in treating disorders relating to behavior, memory (including learning), cardiovascular function, inflammation, sepsis, cardiogenic and hypovolemic shock, sexual dysfunction, penile erection, muscle atrophy, nerve growth and repair, intrauterine fetal growth, and the like.

Although the melanocortin receptor ligands of the present invention are discrete chemical entities, the method of delivery or the method of use may be coupled with other suitable drug delivery systems. For example, a drug delivery technique useful for the compounds of the present invention is the conjugation of the compound to an active molecule capable of being transported through a biological barrier (see e.g. Zlokovic, B.V., *Pharmaceutical Research*, Vol.

12, pp. 1395-1406 (1995)). A specific example constitutes the coupling of the compound of the invention to fragments of insulin to achieve transport across the blood brain barrier (Fukuta, M., et al. *Pharmaceutical Res.*, Vol. 11, pp. 1681-1688 (1994)). For general reviews of technologies for drug delivery suitable for the compounds of the invention see Zlokovic, B.V., *Pharmaceutical Res.*, Vol. 12, pp. 1395-1406 (1995) and Pardridge, WM, *Pharmacol. Toxicol.*, Vol. 71, pp. 3-10 (1992).

PROCEDURES

Functional activity (*in vitro* pre-screening) can be evaluated using various methods known in the art. For example, measurement of the second messenger, cAMP, as described in citation (iv) above, evaluation by Cytosensor Microphysiometer techniques (Boyfield et al. 1996), or by using the compounds of the invention alone, or in combination with natural or synthetic MSH-peptides.

The compounds of the present invention will interact preferentially (i.e., selectively) to MC-4 and/or MC-3, relative to the other melanocortin receptors. Selectivity is particularly important when the compounds are administered to humans or other animals, to minimize the number of side effects associated with their administration. MC-3/MC-4 selectivity of a compound is defined herein as the ratio of the EC_{50} of the compound for an MC-1 receptor ("EC_{50}-MC-1") over the EC_{50} of the compound for the MC-3 (EC_{50}-MC-3) / MC-4 (EC_{50}-MC-4) receptor, the EC_{50} values being measured as described above. The formulas are as follows:

$$\text{MC-3 selectivity} = [EC_{50}\text{-MC-1}] / [EC_{50}\text{-MC-3}]$$

$$\text{MC-4 selectivity} = [EC_{50}\text{-MC-1}] / [EC_{50}\text{-MC-4}]$$

For the purposes of the present invention a receptor ligand (analog) is defined herein as being "selective for the MC-3 receptor" when the above-mentioned ratio "MC-3-selectivity" is at least about 10. In other treatments, methods, or compositions this value is at least about 100, while for yet other embodiments of the present invention the selectivity is at least about 500. A compound is defined herein as being "selective for the MC-4 receptor" when the above-mentioned ratio "MC-4-selectivity" is at least about 10. In other treatments, methods, or compositions this value is at least about 100, while for yet other embodiments of the present invention the selectivity is at least about 500.

All documents cited in the Detailed Description of the Invention are, are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is